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Editorial

The Role of Autoantibodies in Heart Disease

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The production of antibodies as a defense against foreign protein is a concept which has been long established in medical thought and practice. Although on the whole beneficial, the immune reaction may sometimes turn against the individual and give rise to immunopathologic reactions, of which "allergy" is the best known example. Less clearly defined are the pathologic autoimmune reactions which are responsible for a number of human and animal diseases of hitherto unknown etiology.

The inability of an animal to produce antibodies against its own tissues was implicit in Ehrlich's concept of *horror autoxicus*, but as long as 60 years ago, Metalnikoff[1] showed that guinea pigs could produce antibodies active against their own spermatozoa, that is, *autoantibodies*. Similarly, antibodies against the *autoantigens* present in lens, brain, and thyroid have been found. Other organs which may well act as sources of autoantigens are the adrenal, kidney, and skin.[2-4] During the past few years, evidence has accumulated that cardiac tissue, too, can give rise to the production of autoantibodies. How this happens is not clear. The heart is rich in blood and lymph vessels, and thus the theory that the body's mechanism for producing immunity is not normally familiar with the antigens (as has been adduced to explain other autoimmune reactions[5]) is not tenable. One must therefore postulate some change in the antigen pattern of the heart tissue for the body to regard it as "not self" and produce antibodies against it. Such a change may be brought about by streptococcal infection[6] (as in rheumatic heart disease), by cardiac damage[7] (as in the postmyocardial infarction syndrome), or by the adjuvant used in the immunization of experimental animals.

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The concept of autoimmune reaction as etiological cause is accepted for such diseases as thyroiditis[8] and allergic encephalitis.[4] Such acceptance is based on a number of characteristics which must necessarily also apply to those diseases of the heart which are to be explained on an "autoimmune" basis. The characteristics are as follows: (1) In cases in which there is a clear precipitating event, specific symptoms usually appear 2 to 3 weeks later, a period consistent with the production of an immunopathologic response. In addition, such reactions are suppressed by corticosteroids. (2) The pathologic lesions in these diseases show the typical picture of lymphoid granulomatous infiltrations. (3) Evidence of immune reactivity to organ-specific antigens can be found in patients in the form of antibodies in the circulation, skin reactivity, and accumulation of gammaglobulin at the site of the lesion. (4) Diseases similar to those in man can be produced in experimental animals by immunization with appropriate organ antigens. (5) In at least one case,[9] the autoimmune disease can be passively transferred by injection of lymphoid cells from an animal suffering from the disease.

Certain cardiopathies and syndromes fulfill the afore-mentioned criteria, either wholly or partially, and may now be considered in detail.

Rheumatic Heart Disease.—The idea that rheumatic fever might be explained on the basis of sensitization disease "in a focally infected allergic person" was proposed by Zinsser and Yu,[10] in 1928, on the basis of still earlier work. Rich and Gregory[11] demonstrated experimentally that the generalized periarterial infiltrations of kidney, heart, and other organs, characteristic of periarteritis nodosa, were a manifestation of hypersensitivity. Moreover, the injection of homologous (from the same species) heart extracts into various animals, together with foreign serum, caused a concentration of the diffuse infiltrating lesion in the heart, in short, a diffuse myocarditis.[12] It may be recalled that a similar histologic picture is seen in the interstitial myocarditis of patients dying with acute rheumatic fever.[13]

The next step in the chain of evidence was to produce rheumatic-like lesions in experimental animals by injection of homologous heart extracts, and Cavelti[14] claimed to have achieved this, although his work could not be confirmed.[15] During the past few years, however, Kaplan[16] has succeeded in producing myocarditis in animals by immunizing them against heterologous (from other species) heart tissue, and our own results confirm his work.

In experimental animals and sometimes in rheumatic patients, circulating antibodies were found,[18-20] but it was not proved that they were specifically directed against cardiac antigens. This point has now been settled, partly by Kaplan,[21] who found heart-specific insoluble antigens that reacted against patients' sera, and partly by us, who have shown the existence of antibodies against another heart-specific antigen, soluble in saline.[17] Furthermore, it has been demonstrated by immunohistologic methods that such antoantibodies will selectively link up with cardiac tissue,[22] whereas histologic sections of the hearts of patients dying from rheumatic fever show a concentration of gammaglobulin at the site of the lesion.[23]

The role of streptococcal infection in rheumatic heart disease is obscure. We have no clear idea of how this trigger mechanism starts the production of

an autoimmune reaction and causes the specific pathologic lesions, although there is ample clinical and experimental evidence that they are connected.[24,25]

Postcommissurotomy Syndrome.—The attacks of precordial pain and fever described in 10 to 40 per cent of patients 2 to 3 weeks or more after commissurotomy were at first attributed to reactivation of the rheumatic process.[26,27] Against this explanation is the lack of uniform response to salicylates, the absence of serologic evidence of streptococcal infection,[28] and the failure of penicillin prophylaxis.[29] Furthermore, the syndrome has appeared in patients after cardiac operations for congenital heart disease,[30] after simple pericardiotomy,[31] and even after stab wounds of the heart.[32] Corticosteroids are active both in prevention and treatment, and the few fatal cases described showed a nonspecific infiltrative myocarditis.[26,28] It has been suggested that the postcommissurotomy—more properly, the postcardiotomy—syndrome may be an autoimmune reaction consequent to the release of cardiac antigen by surgical trauma,[7] and our finding of circulating heart autoantibodies in a patient after mitral valvotomy confirms this view.[34]

Postmyocardial Infarction Syndrome.—The evidence for ascribing this complication of myocardial infarction to an autoimmunopathologic mechanism is similar to that brought forward in the case of the postcommissurotomy syndrome, which it resembles in many ways.[7] The attacks of pericarditis and pleuritis, the pathologic findings, and the response to cortisone all indicate the presence of a hypersensitivity reaction. We have demonstrated the presence of circulating autoantibodies to heart antigens in two cases. Presumably, the myocardial infarction releases cardiac substances which behave as autoantigens and give rise to the syndrome in 3 to 4 per cent of the cases. We have recently demonstrated moderate to high titers of autoantibody in the sera of three patients who did not develop the syndrome after myocardial infarction.[34]

Other Heart Diseases With Possible Autoimmune Etiology.—There is much evidence of an "allergic" mechanism in the cardiopathies associated with periarteritis nodosa and eosinophilic myocarditis,[35] as well as in disseminated lupus myocarditis.[36] Each of these conditions responds well to cortisone, and each shows the characteristic histologic picture of diffuse round cell infiltration. Typical periarteritis nodosa has been produced in animals,[11] and the lesions could be concentrated in the myocardium.[12] Another condition which may fit into this group is the rheumatoid arthritis heart, which shows focal granulomatous myocarditis in 1 to 3 per cent of the cases,[37] and which may show valvular lesions indistinguishable from (due to ?) rheumatic carditis. In none of these conditions have heart-specific autoantibodies been so far demonstrated, and this group would seem to differ from those diseases already discussed both in the trigger mechanism and the autoimmune process. Endomyocardial fibrosis,[38] a disease of mysterious etiology, might be mentioned in view of the allergic aspects of some cases,[39] although this view is not universally shared.[40] And finally, might not amyloid myocardiopathy share some aspects of an immune disease?

Some Theoretical Considerations.—Heart-specific antigens are present in all mammals that have been tested,[17] and thus the sera of patients react with extracts from the hearts of dogs, rabbits, guinea pigs, and rats as with those

from man. Equally, immunization of animals against heart antigens from the same (homologous) species as well as from other (heterologous) species will yield the specific antiheart antibodies active against all heart antigens, including those from the immune animal itself.

Strictly speaking, proof of the presence of circulating autoantibodies requires demonstration of their activity against the heart of the individual in question. This has been done in animals but not in man, and thus the antibodies in cases of human cardiac disease should properly be referred to as "homoantibodies," that is, reacting with antigens from the same species rather than from the same individual.

The central problem in the explanation of disease pathogenesis by autoimmune reaction is our ignorance of its mechanism. Antigen-antibody reactions are known to have pathologic effects in such allergic diseases as serum sickness, and Masugi's "nephrotoxic sera" produced glomerulonephritic lesions in experimental animals. The finding of specific autoantibodies in sera of patients and animals strengthens the hypothesis that such antibodies may have a pathologic effect, but they are often absent from the circulation or may only be found after the appearance of clinical disease.[34,41] Furthermore, Masugi's sera was heterologous in origin, and attempts to produce autoimmune disease by passive transfer of autoantibodies have met with failure.[41,42] Certain of the collagen diseases may even be common in patients with agammaglobulinemia who lack the ability to produce antibodies.[43]

By analogy with the type of immunity seen in tuberculosis and skin transplantation reactions, a hypothesis of autoimmune disease due to cell-bound antibody has been proposed. The delayed type of skin reaction to intradermal antigen seen in Hashimoto's thyroiditis,[42] and the passive transfer of allergic encephalitis by means of lymphoid cells[9] support this theory. As yet, however, there is no direct evidence of a cell-bound antibody in diseases of the heart. In the light of this hypothesis, however, the presence of circulating autoantibodies is not necessary for the assignment of a disease to the autoimmune category. When such autoantibodies are present, they may be a result rather than a cause of tissue injury.

This is supported by our findings. Experimental animals have shown circulating antiheart antibodies and no cardiac lesions, as have patients with cardiac damage of a nonimmune type, such as cardiotomy and myocardial infarction. The existence of these antibodies, identical in behavior, in the sera of patients with rheumatic heart disease and postmyocardial infarction syndrome may only indicate that they are not pathogenic, and that cardiac damage leaks antigen into the circulation with the same results as the active immunization of experimental animals.

In fact, only a limited number of individuals may have the capacity to produce circulating autoantibodies, as in the case of rheumatic fever, wherein susceptibility is affected by an hereditary (genetic ?) factor.[44,45]

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REFERENCES

1. Metalnikoff, S.: Études sur la spermatoxine, Ann. de l'Inst. Pasteur, Paris **14**:577, 1900.
2. Lessof, M. H., and Asper, S. P.: Autoantibodies, AM. HEART J. **59**:473, 1960.
3. Grabar, P.: Le Problème de l'auto-antigenicité. *In* Grabar, P., and Miescher, P., editors: Immunopathology, First International Symposium, Basel, 1958, p. 20.
4. Waksman, B. H.: Experimental Allergic Encephalomyelitis and the "Auto-Allergic" Diseases, Internat. Arch. Allergy **14** (Suppl.), 1959.
5. Burnet, F. M.: Autoimmune Disease, Brit. M. J. **2**:645 and 720, 1959.
6. Glynn, L. E., and Holborow, E. J.: Conversion of Tissue Polysaccharides to Autoantigens by Group A, Beta Haemolytic Streptococci, Lancet **2**:449, 1952.
7. Dressler, W.: The Post-Myocardial Infarction Syndrome: A Report on Forty-Four Cases, A.M.A. Arch. Int. Med. **103**:28, 1959.
8. Witebsky, E., Rose, N. R., Terplan, K., Paine, J. R., and Egan, K. W.: Chronic Thyroiditis and Autoimmunization, J.A.M.A. **164**:1439, 1957.
9. Paterson, P. Y.: Transfer of Allergic Encephalomyelitis in Rats by Means of Lymph Node Cells, J. Exper. Med. **111**:119, 1960.
10. Zinsser, H., and Yu, H.: The Bacteriology of Rheumatic Fever and the Allergic Hypothesis, Arch. Int. Med. **42**:301, 1928.
11. Rich, A. R., and Gregory, J. E.: The Experimental Demonstration That Periarteritis Nodosa Is a Manifestation of Hypersensitivity, Bull. Johns Hopkins Hosp. **72**:65, 1943.
12. Jaffe, R., and Holz, E.: Experimental Allergic Myocarditis, Exper. Med. & Surg. **6**:189, 1948.
13. Saphir, O., and Langendorf, R.: Nonspecific Myocarditis in Acute Rheumatic Fever, AM. HEART J. **46**:432, 1953.
14. Cavelti, P. A.: Studies on the Pathogenesis of Rheumatic Fever. II. Cardiac Lesions Produced in Rats by Means of Autoantibodies to Heart and Connective Tissue, Arch. Path. **44**:13, 1947.
15. Peck, J. L., and Thomas, L.: Failure to Produce Lesions or Autoantibodies in Rabbits by Injecting Tissue Extracts, Streptococci and Adjuvants, Proc. Soc. Exper. Biol. & Med. **69**:451, 1948.
16. Kaplan, M. H., and Craig, J. M.: Production of Cardiac Lesions in Rabbits Immunized With Heterologous Heart Tissue, Fed. Proc. **17**:520, 1958.
17. Gery, I., Davies, A. M., and Ehrenfeld, E. N.: Heart-Specific Autoantibodies, Lancet **1**:471, 1960.
18. Cavelti, P. A.: Autoantibodies in Rheumatic Fever, Proc. Soc. Exper. Biol. & Med. **60**:379, 1945.
19. Wagner, V., and Rejholec, V.: Response by Antibodies to Tissue Antigen in the Course of Rheumatic Fever, Ann. Rheumat. Dis. **15**:364, 1956.
20. Steffen, C.: Untersuchung und Betrachtung der rheumatischen Erkrankung als Auto-Aggressionskrankheit im Zusammenhang mit disregulierten Abwehrsystemen, Acta neuroveg. **15**:154, 1957.
21. Kaplan, M. H.: Autoantibodies to Heart Tissue in the Sera of Certain Patients With Rheumatic Fever, Fed. Proc. **18**:576, 1959.
22. Kaplan, M. H.: The Fluorescent Antibody Technic as a Research Tool in the Study of Connective Tissue Disease, Arthritis & Rheumatism **2**:568, 1959.
23. Vasquez, J. J., and Dixon, F. J.: Immunohistochemical Study of Lesions in Rheumatic Fever, Systemic Lupus Erythematosus and Rheumatoid Arthritis, Lab. Invest. **6**:205, 1957.
24. Hana, I.: Antimyocardial Autoantibodies in Rabbits Treated Experimentally With Streptococci or With Their Products, J. Hyg. Epid. Microb. & Imm. (Prague) **2**:502, 1958.
25. Morse, S. I., Darnell, J. E., Jr., Thomas, W. A., and Glaser, R. J.: Cardiac Lesions in Rabbits After Pharyngeal Infections With Group A Streptococci, Proc. Soc. Exper. Biol. & Med. **89**:613, 1955.
26. Soloff, L. A., Zatuchni, J., Janton, O. H., O'Neill, T. J. E., and Glover, R. P.: Reactivation of Rheumatic Fever Following Mitral Commissurotomy, Circulation **8**:481, 1953.
27. Dressler, W.: Idiopathic Recurrent Pericarditis, Am. J. Med. **18**:591, 1955.
28. Lisan, P., Reale, A., Harris, T. N., and Likoff, W.: The Postcommissurotomy Syndrome: Incidence and Clinical Pattern Correlated With the Histochemical Analysis of Atrial Tissue and Serologic Studies, Circulation **12**:741, 1955.
29. Epstein, S.: Is the Postcommissurotomy Syndrome of Rheumatic Origin?, A.M.A. Arch. Int. Med. **99**:253, 1957.
30. Ito, T., Engle, M. A., and Goldberg, H. P.: Postpericardiotomy Syndrome Following Surgery for Nonrheumatic Heart Disease, Circulation **17**:549, 1958.
31. Elster, S. K., Wood, H. F., and Seely, R. D.: Clinical and Laboratory Manifestations of the Postcommissurotomy Syndrome, Am. J. Med. **17**:826, 1954.
32. Segal, F., and Tabatznik, B.: Postpericardiotomy Syndrome Following Penetrating Stab Wounds of the Chest: Comparison With the Postcommissurotomy Syndrome, AM. HEART J. **59**:175, 1960.

33. Dressler, W.: A Postmyocardial-Infarction Syndrome. Preliminary Report of a Complication Resembling Idiopathic, Recurrent, Benign Pericarditis, J.A.M.A. **160**:1379, 1956.
34. Ehrenfeld, E. N., Gery, I., and Davies, A. M.: Unpublished data.
35. Reinhart, W.: Isolated Diffuse Interstitial Eosinophilic Myocarditis, Cardiologia **11**:219, 1946.
36. Griffith, G. C., and Vural, I. L.: Acute and Subacute Disseminated Lupus Erythematosus. A Correlation of Clinical and Postmortem Findings in Eighteen Cases, Circulation **3**:492, 1951.
37. Sokoloff, L.: The Heart in Rheumatoid Arthritis, Am. Heart J. **45**:635, 1953.
38. Ball, J. D., Williams, A. W., and Davies, J. N. P.: Endomyocardial Fibrosis, Lancet **1**:1049, 1954.
39. Lynch, J. B., and Watt, J.: Diffuse Endomyocardial Sclerosis, Brit. Heart J. **19**:173, 1957.
40. Arnott, W. M.: A Problem in Tropical Cardiology, Brit. M. J. **2**:1273, 1959.
41. Doniach, D., Hudson, R. V., and Roitt, I. M.: Human Autoimmune Thyroiditis: Clinical Studies, Brit. M. J. **1**:365, 1960.
42. Witebsky, E., Paine, J. R., and Rose, N. R.: Clinical Significance of Autosensitization to Thyroglobulin. *In* Grabar, P., and Miescher, P., editors: Immunopathology, First International Symposium, Basel, 1958, p. 162, and discussion, p. 180.
43. Good, R. A.: Rheumatoid Arthritis and Agammaglobulinemia, Bull. Rheumat. Dis. **10**:203, 1960.
44. Wilson, M. G., and Schweitzer, M.: Pattern of Hereditary Susceptibility in Rheumatic Fever, Circulation **10**:699, 1954.
45. Davies, A. M., and Lazarov, E.: Heredity, Infection and Chemoprophylaxis in Rheumatic Carditis, J. Hyg. **58**:1960.

Clinical Communications

A Qualitative and Quantitative Study of the Ventricles and Great Vessels of Normal Children

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INTRODUCTION

It is a common observation that the electrocardiographic patterns and radiologic images derived from the hearts of normal adults differ significantly from those derived from the hearts of normal children. In the present era of rapid advancements in the surgical correction of cardiac deformities, the need for precise anatomic diagnosis of both acquired and congenital cardiopathies in children is obvious. Thus, an anatomic study of the ventricles and great vessels of normal children was undertaken in an effort to qualify and classify the above-mentioned differences. Since few studies of this particular type have been made, we hoped also that our "base line" definitions might provide information which would permit further understanding of various aspects of cardiopathies in children.

In this paper we present the findings of a study of the hearts of 100 normal children who represented all age groups, i.e., premature, postnatal, early childhood, and puberty. Special attention was paid to the following observations and measurements: thickness of the free walls of both ventricles, circumferences of the atrioventricular orifices and of the orifices of the great vessels, length of the trunks of the great vessels and the infundibulum of the pulmonary artery. We also calculated the area of the mitral and tricuspid valves and the diameter of the aortic and pulmonary orifices. The observations were correlated with the age of the children and submitted to statistical analysis.

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MATERIAL AND METHOD

One hundred normal unfixed hearts were studied; they were obtained from autopsies made at the Hospital Infantil of Mexico City. The children from whom the hearts were taken ranged in age from prematurity (6 months of intrauterine life) to 12 years.

Selection of the normal hearts was made on the basis of careful clinical, anatomic, and histologic studies. Thus, we eliminated all hearts with congenital deformities and those in which the myocardium was affected by infectious or degenerative processes.

Consideration was given to the age, sex, height, and weight of each child, as well as to the diagnosis of the illness that caused death.

The hearts were grouped according to the age of the child, in the following manner: one group which consisted of hearts from premature infants, and twelve groups, one for each year of life (the last group included the heart of one child who was 13 years of age). In addition, the age group of 1 year was subdivided into seven groups, one for each month of the first 6 months of life and one for age 6-12 months. If the age of a given child was 2 years or 2 years and 11 months, the heart from that child was included in the group of 2-3 years. If, however, a child was just 3 years old or slightly older, the heart from that child was then placed in the group of 3-4 years.

In all instances we observed the condition of the papillary muscles, the chordae tendineae, and the valve leaflets and cusps. Finally, the following anatomic elements were carefully measured: (1) thickness of the ventricular walls, (2) inflow and outflow tracts of both ventricles, (3) atrioventricular orifices and orifices of the great vessels, (4) circumference of the trunks of the great vessels and length of the trunk of the pulmonary artery, and (5) infundibulum of the pulmonary artery.

1. *Thickness of the Ventricular Walls (mm.).*—This measurement excluded the papillary muscles and the trabecular tissue. The sites of measurement in the right ventricle were the anterior, lateral, and posterior borders.* Each border was divided into horizontal thirds, and the middle of each third was measured. The largest measurement so obtained from each border was then used for the statistical analysis. In addition, we also measured the anterior wall of the infundibulum and again used the largest figure. Thus, we had four measurements from the right ventricle.

For the left ventricle we measured the anterior, lateral, and posterior borders,† in a manner similar to that used for the right ventricle. The largest measurement of each border was used for the final analysis.

2. *Inflow and Outflow Tracts of Both Ventricles (mm.).*—The inflow tract of the right ventricle was measured as extending from the insertion of the septal leaflet of the tricuspid valve to the apex of the right ventricle. The outflow tract was measured from the same apex to the annulus of the pulmonary artery at the site of insertion of the posterior cusps of the pulmonary valve.

The inflow tract of the left ventricle was measured as extending from the insertion of the aortic leaflet of the mitral valve to the apex of the left ventricle. The outflow tract was measured from the same apex to the insertion in the annulus of the anterior cusps of the aortic valve.

3. *The Atrioventricular Orifices and the Orifices of the Great Vessels (mm.).*—The circumferences of these orifices were measured after the hearts were opened. In the mitral and tricuspid orifices the measurements were made at the level of the annulus where the valve leaflets inserted. In the great vessels also the measurements were made at the annulus where the cusps inserted. Then the circumference was used to calculate the areas of the A-V orifices, and the diameters of the orifices of the great vessels were also derived from the appropriate circumferences.

4. *Circumference of the Trunks of the Great Vessels and Length of the Trunk of the Pulmonary Artery (mm.).*—The circumferences of the trunks of the pulmonary artery and the ascending portion of the aorta were measured in several sites. The length of the trunk of the pulmonary

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***Right Ventricle.*—Anterior border: junction of the anterior wall with the septum. Posterior border: junction of the posterior wall with the septum. Lateral border: free right ventricular wall in the region of the right marginal artery.**

†Left Ventricle.*—Anterior border: junction of the anterior wall with the septum. Posterior border: junction of the posterior wall with the septum. Lateral border: free left ventricular wall in the region of the left marginal artery.

artery was measured from the junction of the right ventricular wall with the wall of the pulmonary artery to the bifurcation of this vessel.

5. *Infundibulum of the Pulmonary Artery.*—The length of the infundibulum was measured from the inferior border of the parietal portion of the crista supraventricularis (free wall) to the insertion of the cusps of the pulmonary valve. The inferior circumference of the infundibulum was measured in the imaginary horizontal plane which originates at the inferior border of the crista supraventricularis and passes through the adjacent septum and the free wall of the right ventricle. The important reference point for this measurement is the inferior border of the crista supraventricularis, which can be easily located in normal hearts. The diameter was derived from this circumference. The thickness of the crista was that measured at the inferior or free border of the parietal portion.

In each group the mean value was calculated from the observed measurements. This mean, or average, which is the most representative value for the series of data, was calculated as usual by dividing the total sum of the measurements by the number of measurements. The averages were tabulated and graphed in order to depict more clearly the variations of growth in relation to age. In some of the tables, minimum and maximum as well as mean values are given in order to show the range that exists within the groups. When the range is great, obviously the mean has less significance than when the range is small. This criterion must be kept in mind when drawing conclusions for each group.

Since we were also interested in the relationship between the growth of the annulus of the pulmonary artery and the inferior circumference of the infundibulum, we calculated the correlation coefficient between them. This is a statistical parameter that indicates whether or not a definite relationship exists between two series of data. If the coefficient approaches unity, a significant relationship may be said to exist, and as the relationship becomes less significant, the value of the coefficient approaches zero.

RESULTS AND DISCUSSION

I. *Variations in the Thickness of the Walls of the Right and Left Ventricles in Relation to Age.*—

A. *Left ventricle:* The statistical analysis for the cases during the first year of life (months) shows that in spite of some minor variations the thickness of the left ventricle increases with age (Fig. 1). The same conclusion also applies from the second year through the twelfth year of life. As may be seen from Fig. 1, this increase is quite marked.

From the calculated means for each of the borders of the left ventricle it may be seen that the lateral border obtains the greatest thickness, and shows as well the greatest increase in thickness in relation to age when compared to the other borders of the left ventricle (Fig. 2). The majority of the largest measurements were found in the highest portions of the left ventricle.

B. *Right ventricle:* The thickness of the wall of the right ventricle increases very slightly in the first year of life (studied by months), as may be seen in Fig. 1. The right ventricular thickness also increases very little from the age of 2 years through the age of 12 years. The thickness of the right ventricular wall is less than that of the left in the hearts of premature infants, in the hearts of postnatal infants, and, in general, in the majority of the hearts of the children who were studied, as may be observed in Fig. 1 (see also Fig. 6, *A-D*).

We observed that both ventricles increase in thickness with age. However, this increase was discordant because of the much greater increase in the left ventricle as compared to the slight increase in the right ventricle.

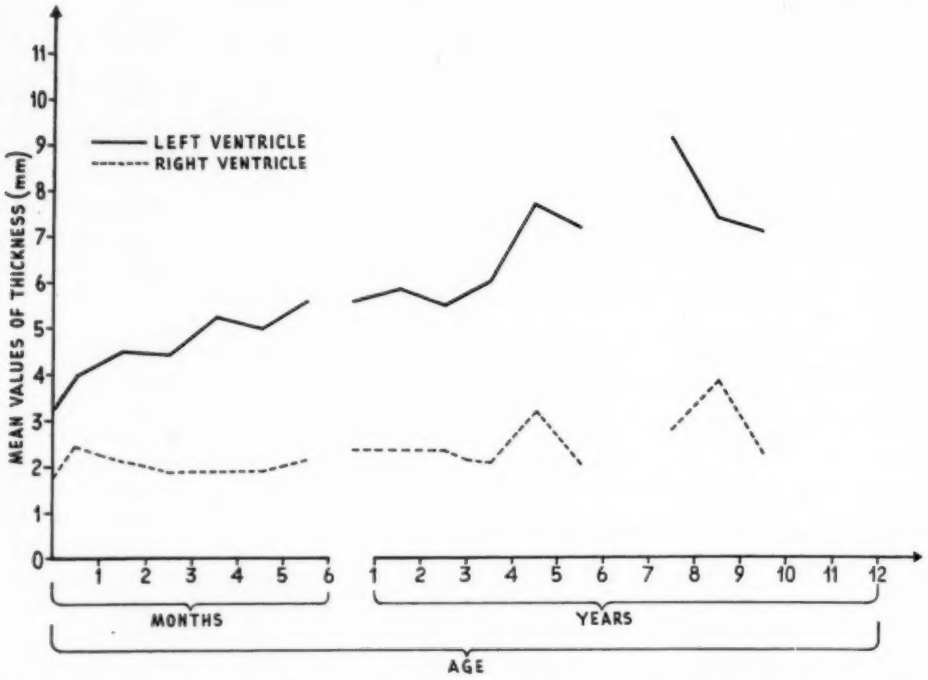

Fig. 1.—Mean thickness of the free walls of the ventricles in normal children of different ages.

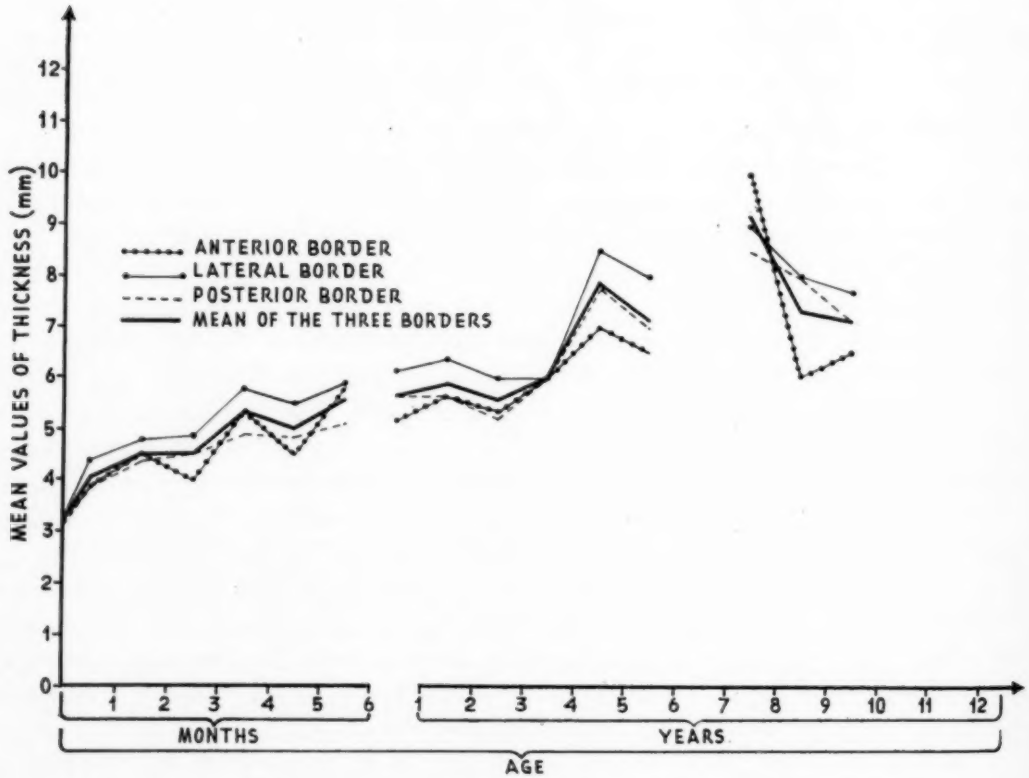

Fig. 2.—Mean thickness of the different borders of the free wall of the left ventricle in normal children of different ages.

The mean thickness of the left ventricle was seen to be, in general, more than double that of the right ventricle (Fig. 1). This is contrary to the classic opinion[1-5] which holds that there is equality of both ventricles, or physiologic hypertrophy of the right ventricle, in children. We found the right ventricle always to be thinner than the left, from 6 months of intrauterine life to 12 years.

In regard to the thickest portion of the right ventricle, we encountered great variation and cannot draw any conclusion on this point.* The thinnest area was clearly the anterior border (Fig. 3). Finally, in Table I the means of each of the borders of the right and left ventricular wall at different ages are given. These were calculated from the maximum measurements of each border. Table I shows as well the mean for the entire right and left ventricular wall as calculated from the means of the borders of each wall.

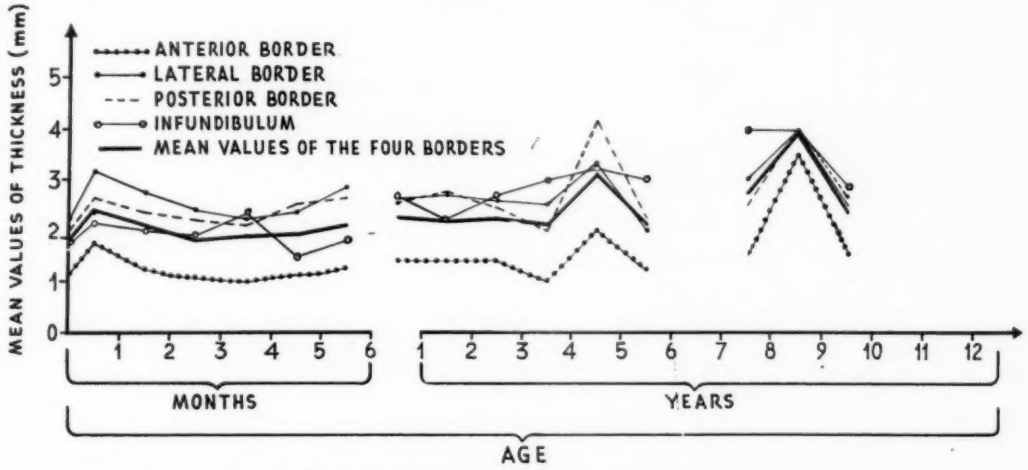

Fig. 3.—Mean thickness of the different borders of the free wall of the right ventricle and the infundibulum in normal children of different ages.

II. *Variations in the Length of the Inflow and Outflow Tracts of the Ventricles in Relation to Age.*—The results of the statistical analysis of these measurements are given in Table II and Fig. 4. The outflow tract of the right ventricle was the longest, grew more, and was the most uniform in its growth. On the other hand, the inflow tract of the right ventricle was, in general, the shortest and grew the least when compared with the other tracts. It also showed more variation in its longitudinal growth.

The other two tracts grew in a manner which was more or less similar, and we noted that the lengths of the two tracts of the left ventricle were unevenly distributed between the measurements of the outflow and inflow tracts of the right ventricle.

Table II shows the minimum, maximum, and mean values of the inflow and outflow tracts of both ventricles, as well as the number of hearts in each age group. These values could be used for valid pathologic comparison if they are taken with the reservation that some groups include only a few hearts and therefore their statistical value is not highly significant.

*It is our impression that the greatest thickness of the free right ventricular wall is found either at the highest portion of the posterior border or at the highest portion of the lateral border.

TABLE I. MEAN THICKNESS (MM.) OF DIFFERENT BORDERS OF THE FREE VENTRICULAR WALLS, 100 HEARTS

AGE	NUMBER OF HEARTS	LEFT VENTRICLE				RIGHT VENTRICLE				
		ANTERIOR	LATERAL	POSTERIOR	MEAN OF THREE	ANTERIOR	LATERAL	POSTERIOR	INFUNDIBULUM	MEAN OF FOUR
Prematures	6	3.25	3.33	3.16	3.25	1.17	2.25	2.00	1.75	1.79
Months										
0–1	16	3.84	4.34	3.84	4.00	1.75	3.19	2.59	2.15	2.42
1–2	6	4.50	4.75	4.42	4.55	1.25	2.75	2.33	2.00	2.08
2–3	5	4.00	4.80	4.50	4.43	1.10	2.40	2.20	1.90	1.90
3–4	4	5.37	5.75	4.87	5.33	1.00	2.20	2.12	2.35	1.92
4–5	3	4.50	5.50	4.83	4.94	1.16	2.33	2.50	1.50	1.87
5–6	5	5.80	5.90	5.10	5.60	1.30	2.80	2.60	1.80	2.12
6–12	13	5.15	6.07	5.58	5.60	1.46	2.58	2.54	2.58	2.29
Years										
1–2	22	5.57	6.34	5.61	5.84	1.45	2.70	2.73	2.29	2.29
2–3	7	5.28	6.00	5.21	5.49	1.43	2.64	2.43	2.57	2.27
3–4	1	6.00	6.00	6.00	6.00	1.00	2.50	2.00	3.00	2.12
4–5	2	7.00	8.50	7.75	7.75	2.00	3.25	4.25	3.25	3.19
5–6	2	6.50	8.00	7.00	7.16	1.25	2.00	2.25	3.00	2.12
6–7	0									
7–8	1	10.00	9.00	8.50	9.16	1.50	3.00	2.50	4.00	2.75
8–9	1	6.00	8.00	8.00	7.33	3.50	4.00	4.00	4.00	3.87
9–10	4	6.50	7.75	7.12	7.12	1.50	2.37	2.50	2.87	2.31
10–11	0									
11–12	2	9.50	12.75	10.50	10.91	2.50	4.75	5.00	3.50	3.94

TABLE II

AGE	NUMBER OF HEARTS	RIGHT VENTRICLE (MM.)						LEFT VENTRICLE (MM.)					
		INFLOW TRACT			OUTFLOW TRACT			INFLOW TRACT			OUTFLOW TRACT		
		MINIMUM	MAXIMUM	MEAN	MINIMUM	MAXIMUM	MEAN	MINIMUM	MAXIMUM	MEAN	MINIMUM	MAXIMUM	MEAN
Prematures	6	15.00	27.00	20.66	20.00	30.00	24.66	16.00	26.50	21.75	18.00	26.00	22.83
Years													
0–1	52	16.00	39.00	27.54	20.00	45.00	33.33	15.00	45.00	28.02	20.00	42.00	30.50
1–2	22	25.00	45.00	32.04	33.00	57.00	39.18	24.00	42.00	33.23	26.00	47.00	35.36
2–3	7	30.00	40.00	35.86	36.00	47.00	41.57	35.00	41.00	37.00	36.00	41.00	38.86
3–4	1	41.50	41.50	41.50	45.00	45.00	45.00	35.00	35.00	35.00	36.00	36.00	36.00
4–5	2	38.00	45.00	41.50	50.00	52.00	51.00	44.00	46.00	45.00	49.00	50.00	49.50
5–6	2	47.00	48.00	47.50	51.00	56.00	55.00	42.00	44.00	43.00	46.00	46.00	46.00
6–7	0	———	———	———	———	———	———	———	———	———	———	———	———
7–8	1	52.00	52.00	52.00	56.00	56.00	56.00	50.00	50.00	50.00	55.00	55.00	55.00
8–9	1	57.00	57.00	57.00	65.00	65.00	65.00	48.00	48.00	48.00	50.00	50.00	50.00
9–10	4	45.00	63.00	59.67	49.00	75.00	67.33	46.00	60.00	58.67	43.00	63.00	58.33
10–11	0	———	———	———	———	———	———	———	———	———	———	———	———
11–12	2	49.00	65.00	———	65.00	82.00	———	56.00	71.00	———	52.00	75.00	———

III. *The Atrioventricular Orifices and the Orifices of the Great Vessels (Table III).**—

A. *Mitral:* The circumference of the mitral orifice in the group of hearts from premature infants had a minimum value of 20 mm., a maximum of 36 mm., and a mean of 27.17 mm. These values increased up to and including the hearts in the age group of 11-12 years, in which the minimum was 71 mm., the maximum was 85 mm., and the mean was 78 mm.

The mean area of the mitral valve in the premature group was 0.59 $cm.^2$, and in the age group of 11-12 years a value of 4.84 $cm.^2$ was reached.

B. *Tricuspid:* The circumference of the tricuspid orifice in the premature group had a minimum value of 24 mm., a maximum of 32 mm., and a mean of 28.33 mm. These values increased, with certain variations, in each one of the age groups until in the age group of 11-12 years the minimum was 82 mm., the maximum was 110 mm., and the mean was 96 mm.

The mean area of the tricuspid orifice was 0.66 $cm.^2$ in the premature group and increased to a value of 7.33 $cm.^2$ in the age group of 11-12 years.

Thus, the circumference and area of the mitral valve were always less than that of the tricuspid valve.

C. *Aorta:* In the premature group the minimal circumference of the aortic valve orifice was 15 mm., the maximum value was 21 mm., and the mean was 17.33 mm. In the age group of 11-12 years the minimum was 45 mm., the maximum was 46 mm., and the mean was 45.5 mm. The mean of the diameter of this orifice was 0.55 cm. for the premature group, and reached a value of 1.45 cm. for the 11-12-year-old group.

D. *Pulmonary artery:* In the premature group the circumference of the orifice of the pulmonary artery had a minimum value of 15 mm., a maximum of 22 mm., and a mean of 18.5 mm. In the age group of 11-12 years the minimum was 50 mm., the maximum was 52 mm., and the mean was 51. The means of the diameter of this orifice for the two groups were 0.59 and 1.65 cm., respectively.

As general conclusions to the observations shown in Table III, we can deduce that there is an increase in the orifices of the atrioventricular openings and the orifices of the great vessels in relation to age, despite the variations that exist within each group as well as between the different groups. We also note that the tricuspid opening is larger than the mitral opening, and that the pulmonary orifice is larger than that of the aorta.

IV. *Study of the Trunk of the Pulmonary Artery and the Ascending Portion of the Aortic Arch (Table IV).*—

A. *Circumference of trunk of pulmonary artery:* Table IV shows the minimum, maximum, and the mean values of the circumference of the trunk of the pulmonary artery in different age groups. In the 6 premature infants the minimum was 14 mm., the maximum was 28 mm., and the mean was 20.16 mm. In the age group of 11-12 years the minimum was 45 mm., the maximum was 53 mm., and the mean was 49 mm. We observed that the growth was not very uniform

*The measurements given above and in the remainder of the paper refer only to the first group, the hearts from premature infants, and the last group, hearts from children aged 11-12 years. The tables should be consulted for the measurements of the other age groups.

in the older age groups, which could be partially accounted for by the smaller number of hearts included in some of those groups.

B. *Length of trunk of pulmonary artery:* We observed a minimum of 2 mm., a maximum of 4 mm., and a mean of 2.66 mm. for the premature group, and for the age group of 11-12 years the minimum value was 9 mm., the maximum was 11 mm., and the mean was 10 mm.

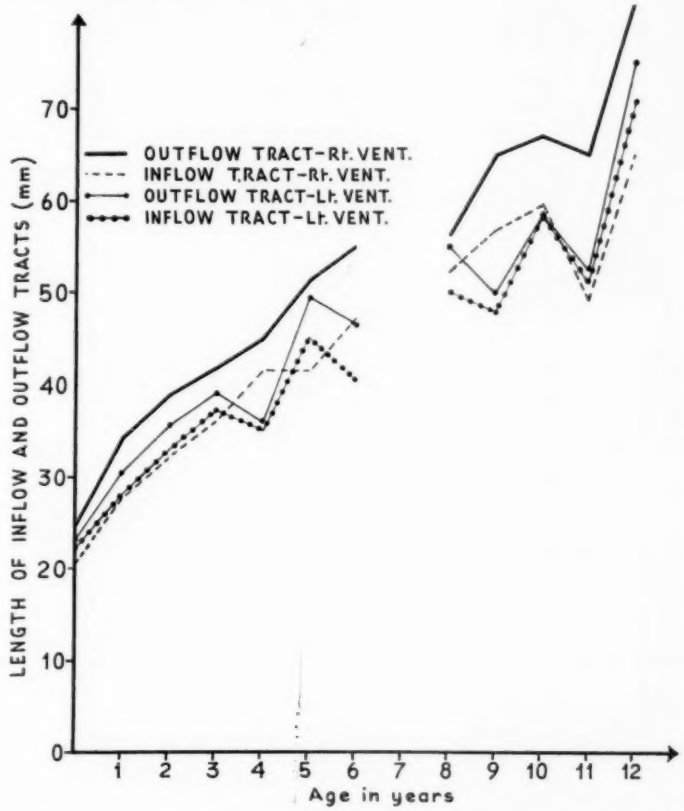

Fig. 4.—Variation in longitudinal growth, in relation to age, of the inflow and outflow tracts of both ventricles in normal children.

C. *Circumference of trunk of aorta:* The hearts of the premature group showed a minimum value of 14 mm., a maximum of 18 mm., and a mean of 16 mm. In the hearts of the 11 to 12-year group the minimum was 46 mm., the maximum was 47 mm., and the mean was 46.5 mm. In general, we are able to say that the circumference of the trunk of the pulmonary artery as well as the length increases with age, even though there is again variability within and between the groups. Also, the circumference of the trunk of the pulmonary artery is greater than that of the aorta.

V. *Study of the Infundibulum of the Pulmonary Artery (Table V).—*

A. *Length of infundibulum:* In the hearts of the group of premature infants this measurement had a minimum value of 3 mm., a maximum of 5 mm., and a mean of 4 mm. The length of the infundibulum in the 2 hearts from the children in the age group of 11-12 years was 15 mm.

TABLE III

AGE	NUMBER OF HEARTS	CIRCUMFERENCE OF MITRAL ORIFICE (MM.)				CIRCUMFERENCE OF TRICUSPID ORIFICE (MM.)				CIRCUMFERENCE OF AORTA (ANNULUS) (MM.)				CIRCUMFERENCE OF PULMONARY ARTERY (ANNULUS) (MM.)			
		MINIMUM	MAXIMUM	MEAN	MEAN AREA (CM.²)	MINIMUM	MAXIMUM	MEAN	MEAN AREA (CM.²)	MINIMUM	MAXIMUM	MEAN	MEAN DIAMETER (CM.)	MINIMUM	MAXIMUM	MEAN	MEAN DIAMETER (CM.)
Prematures	6	20	36	27.17	0.59	24	32	28.83	0.66	15	21	17.33	0.55	15	22	18.50	0.59
Months																	
0–1	16	21	39	31.56	0.79	26	46	35.37	0.99	15	25	19.44	0.62	16	26	21.94	0.69
1–2	6	30	41	34.33	0.94	33	45	39.33	1.23	15	26	22.00	0.70	20	29	24.66	0.78
2–3	5	27	36	32.40	0.83	34	41	37.60	1.12	20	27	22.40	0.71	21	29	23.40	0.74
3–4	4	36	50	40.50	1.30	43	57	47.75	1.81	24	33	28.50	0.91	25	34	29.75	0.94
4–5	3	36	46	40.66	1.31	45	53	48.66	1.88	24	28	25.66	0.82	27	32	28.66	0.91
5–6	5	37	47	41.20	1.35	41	55	49.00	1.91	24	31	27.40	0.87	26	34	30.60	0.97
6–12	13	35	44	40.31	1.29	41	56	50.31	2.01	25	32	28.54	0.91	24	36	30.92	0.98
Years																	
1–2	22	36	60	45.09	1.62	45	72	53.95	2.31	27	42	31.91	1.01	30	41	34.36	1.09
2–3	7	41	50	43.71	1.52	45	57	53.43	2.27	29	35	32.14	1.10	32	35	34.14	1.08
3–4	1	55	55	55.00	2.41	64	64	64.00	3.26	37	37	37.00	1.18	41	41	41.00	1.30
4–5	2	60	71	65.50	3.41	80	80	80.00	5.09	41	45	43.00	1.37	42	45	43.50	1.38
5–6	2	57	62	59.50	2.82	65	75	70.00	3.90	39	40	39.50	1.26	40	42	41.00	1.30
6–7	0	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
7–8	1	65	65	65.00	3.36	82	82	82.00	5.35	43	43	43.00	1.37	55	55	55.00	1.75
8–9	1	70	70	70.00	3.90	87	87	87.00	6.02	42	42	42.00	1.33	50	50	50.00	1.59
9–10	4	60	84	71.75	4.09	76	104	89.25	6.64	40	50	45.00	1.43	40	53	46.50	1.48
10–11	0	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
11–12	2	71	85	78.00	4.84	82	110	96.00	7.33	45	46	45.50	1.45	50	52	51.00	1.65

TABLE IV

AGE	NUMBER OF HEARTS	CIRCUMFERENCE OF TRUNK OF PULMONARY ARTERY (MM.)			LENGTH OF TRUNK OF PULMONARY ARTERY (MM.)			CIRCUMFERENCE OF TRUNK OF AORTA (MM.)		
		MINIMUM	MAXIMUM	MEAN	MINIMUM	MAXIMUM	MEAN	MINIMUM	MAXIMUM	MEAN
Prematures	6	14	28	20.16	2	4	2.66	14	18	16.00
Months										
0–1	16	13	25	20.87	2	5	3.56	14	23	18.00
1–2	6	19	30	24.00	3	5	4.33	19	26	21.66
2–3	5	20	29	23.60	2	5	4.00	16	26	21.60
3–4	4	24	31	28.75	4	6	4.75	25	31	27.00
4–5	3	26	30	28.00	4	5	4.66	24	30	26.33
5–6	5	26	35	30.60	5	5	5.00	24	31	27.00
6–12	13	21	40	31.54	4	6	4.92	22	33	28.00
Years										
1–2	22	29	44	33.82	4	7	5.00	26	42	30.68
2–3	7	35	40	36.28	5	9	5.57	29	36	32.00
3–4	1	41	41	41.00	5	5	5.00	35	35	35.00
4–5	2	43	46	44.50	5	7	6.00	41	46	43.50
5–6	2	36	38	37.00	5	7	6.00	37	48	42.50
6–7	0	—	—	—	—	—	—	—	—	—
7–8	1	50	50	50.00	10	10	10.00	40	40	40.00
8–9	1	44	44	44.00	9	9	9.00	37	37	37.00
9–10	4	43	50	46.50	8	10	8.50	36	49	42.00
10–11	0	—	—	—	—	—	—	—	—	—
11–12	2	45	53	49.00	9	11	10.00	46	47	46.50

TABLE V

AGE	NUMBER OF HEARTS	LENGTH OF INFUNDIBULUM (MM.)				INFERIOR CIRCUMFERENCE OF INFUNDIBULUM (MM.)				THICKNESS OF CRISTA SUPRAVENTRICULARIS (MM.)		
		MINIMUM	MAXIMUM	MEAN	%*	MINIMUM	MAXIMUM	MEAN	MEAN DIAMETER (CM.)	MINIMUM	MAXIMUM	MEAN
Prematures	6	3	5	4.00	16.44	18	33	28.58	0.91	2	3	2.58
Months												
0–1	16	3	8	5.19	18.70	20	44	31.25	0.99	2	5	3.47
1–2	6	3	6	5.33	16.32	33	45	37.25	1.18	3	4	3.33
2–3	5	3	6	4.60	14.56	30	40	33.60	1.07	3	4	3.40
3–4	4	5	8	6.50	17.68	40	45	42.75	1.36	3	5	3.75
4–5	3	6	9	7.00	17.94	38	49	43.66	1.39	3	8	4.66
5–6	5	4	8	5.20	13.75	31	55	44.20	1.41	3	5	4.20
6–12	13	5	10	6.46	17.42	33	54	43.23	1.37	2	6	4.00
Years												
1–2	22	3	9	6.45	16.46	28	60	44.04	1.40	3	6	3.82
2–3	7	6	9	7.43	17.87	43.5	50	46.07	1.46	3	10	4.50
3–4	1	6	6	6.00	13.33	61	61	61.00	1.94	4	4	4.00
4–5	2	8	10	9.00	17.65	61	72	66.50	2.12	5	9	7.00
5–6	2	6	10	8.00	14.95	59	60	59.50	1.89	3	3.5	3.25
6–7	0	—	—	—	—	—	—	—	—	—	—	—
7–8	1	8	8	8.00	14.28	71	71	71.00	2.26	5	5	5.00
8–9	1	15	15	15.00	23.07	70	70	70.00	2.23	5	5	5.00
9–10	4	9	11	10.00	15.94	65	78	70.25	2.23	4	5	4.75
10–11	0	—	—	—	—	—	—	—	—	—	—	—
11–12	2	15	15	15.00	20.40	64	87	75.50	2.40	5	8	6.50

*Percentage of the outflow tract of the right ventricle comprised by the infundibulum.

We observed that the growth was not very uniform in relation to age. Thus, in some groups it decreased; however, this does not negate the conclusion that the length increases with age, since the decreases were probably due to the inclusion of fewer hearts in those groups.

We also investigated whether or not a relationship exists between the length of the infundibulum of the pulmonary artery and the length of the outflow tract of the right ventricle. This is seen in Table V, wherein the percentage of one in respect to the other is given for each age group. We found that the proportion between the length of the infundibulum and that of the outflow tract of the right ventricle varied very little for the different age groups. Thus, the growth of both structures was more or less parallel and proportional.

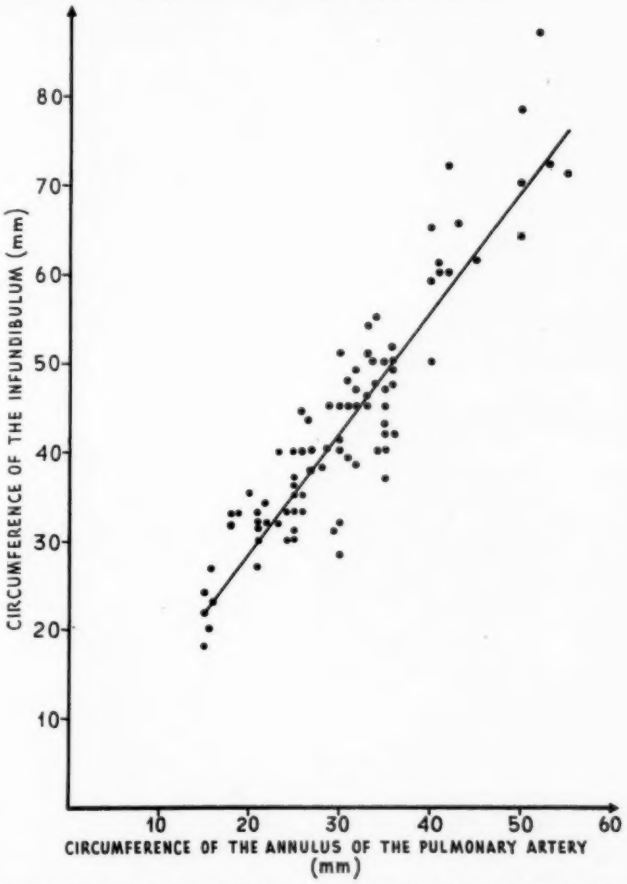

Fig. 5.—Relationship between the inferior circumference of the infundibulum and that of the annulus of the pulmonary artery in normal children.

B. *Inferior circumference of infundibulum:* The group of premature hearts had a minimum value of 18 mm., a maximum of 33 mm., and a mean of 28.58 mm. The hearts in the age group of 11-12 years had a minimum value of 64 mm., a maximum of 87 mm., and a mean of 75.5 mm.

The mean of the diameter of the inferior circumference of the infundibulum was 0.91 cm. for the premature group, and reached a value of 2.4 cm. for the 11 to 12-year group.

C. *Thickness of crista supraventricularis:* In the hearts from the premature infants we found a minimum value of 2 mm., a maximum of 3 mm., and a mean of 2.58 mm. In the hearts from the 11 to 12-year-old children the minimum was 5 mm., the maximum was 8 mm., and the mean was 6.5 mm. The growth was very variable.

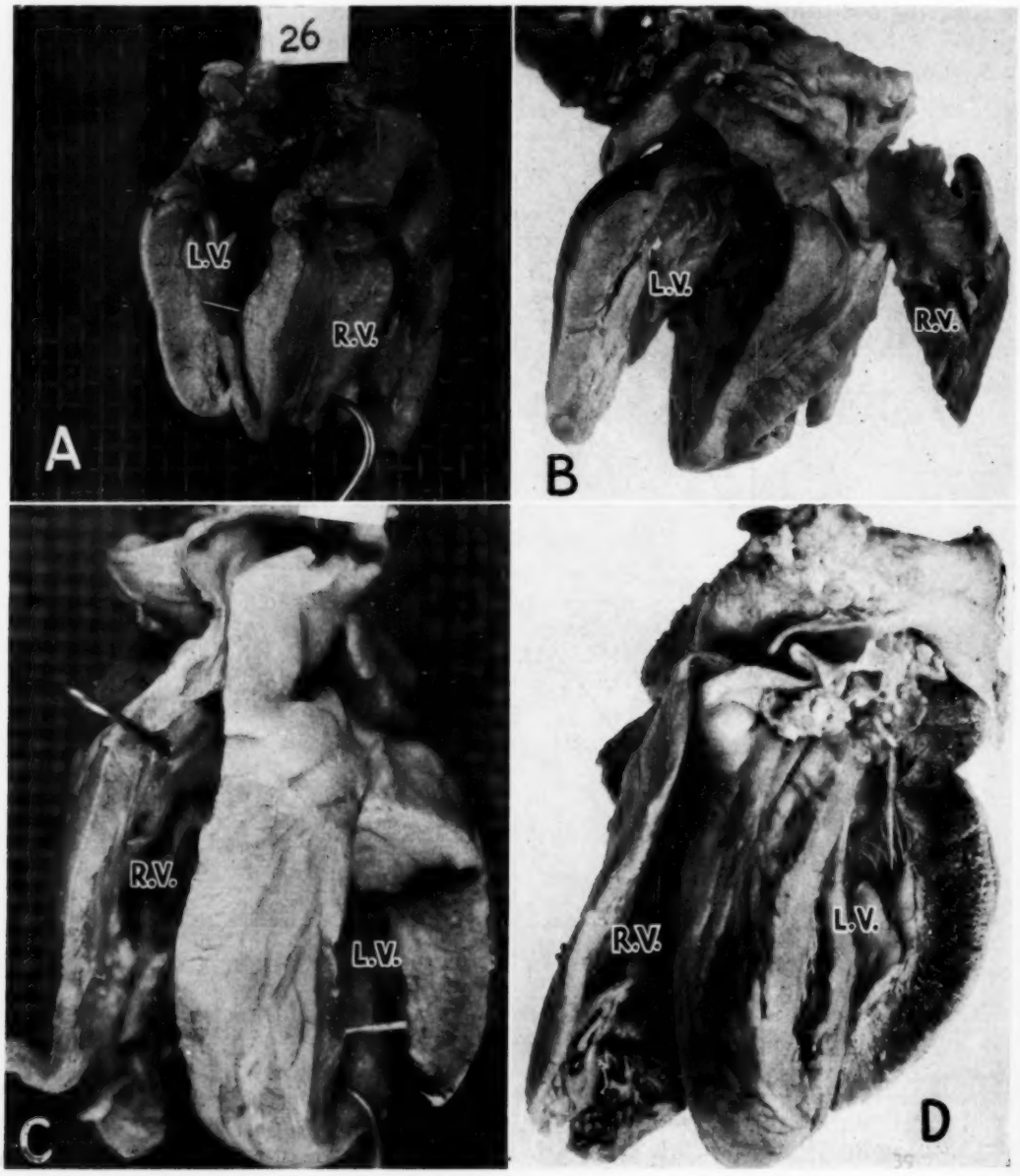

Fig. 6.—Hearts of normal children of different ages, with the ventricles opened, demonstrating the greater thickness of the wall of the left ventricle in relation to the thickness of the wall of the right ventricle. *A*, Posterior view: Premature at 7 months. *B*, Posterior view: full-term, age 1 day. *C*, Anterior view: age 1 year and 6 months. *D*, Anterior view: age 13 years. *RV*: Right ventricle. *LV*: Left ventricle.

D. *Correlation between inferior circumference of infundibulum and circumference of annulus of valve of pulmonary artery:* We calculated the correlation coefficient for the 100 hearts studied, in order to investigate whether or not a relationship existed between the two circumferences. We assigned to the values of the circumference of the annulus of the pulmonary artery the variable x. Variable y was then taken to be the values of the inferior circumference of the infundibulum. After making the necessary calculations, we found that the coefficient had a value of 0.91. As may be observed in Fig. 5, the correlation is direct; that is to say, as the size of the annulus increases, the size of the circumference of the infundibulum increases proportionally. The increase in the latter is approximately 36 per cent more than the increase in the pulmonary orifice.

In order to be more certain of the results of this correlation, we subjected the regression coefficient b of the adjusted line to the t-test of Student. We found that these results were real, not apparent, inasmuch as the calculated value of t was 2.19, and theoretically, with 98 degrees of freedom and a 5 per cent probability of error the value of t is 1.98.

We also investigated whether the coefficient of correlation was real or apparent and found that it was indeed real. Thus we can state that this correlation is highly significant.

Since the values used for these calculations may be of some interest, we give them here: Mean of x: 30.85. Mean of y: 43.27. Coefficient of regression b: 1.36. Value of a (slope of the line): 1.31. Standard error: 28.39. Standard deviation of y: 166.20.

SUMMARY

1. One hundred unfixed normal hearts were studied from children whose ages ranged from 6 months of intrauterine life to 12 years. Criteria of normality were established which were based on the anatomic and histologic examination of these hearts. All of the measurements obtained were analyzed statistically.

2. The thickness of the walls of both ventricles increased with age. This increase in thickness was marked in the left ventricle and slight in the right ventricle. The wall of the right ventricle was always thinner than that of the left in the hearts of premature infants, in the hearts of newborn infants, and, in general, in all of the hearts studied. In the left ventricle the portion that reached the greatest thickness was the lateral border, and in the right ventricle the portion that was the thinnest was the anterior border.

3. The study of the longitudinal growth of the ventricular outflow tracts showed that the largest tract as well as that which grew the most was the outflow tract of the right ventricle. The smallest tract and that which grew the least was the inflow tract of the same ventricle.

4. The circumferences of the atrioventricular orifices, and the circumferences of the orifices of the great vessels increase with age. The circumference and the area of the tricuspid orifice were greater than those of the mitral orifice. The diameter and the circumference of the orifice of the pulmonary artery were greater than those of the aorta.

5. The circumference of the trunk of the pulmonary artery and the circumference of the ascending portion of the arch of the aorta increase with age. The length of the trunk of the pulmonary artery also increases with age. In general, the circumference of the pulmonary artery was greater than that of the aorta.

6. The length of the infundibulum of the pulmonary artery increases with age and in a manner parallel to the increase in the outflow tract of the right ventricle. The annulus of the valve of the pulmonary artery increased proportionally in relation to the inferior circumference of the infundibulum. The increase in the latter was 36 per cent greater than the increase in the valvular orifice of the pulmonary artery.

We are greatly indebted to Dr. M. Salas Martínez, Chief of the Department of Anatomy-Pathology of the Hospital Infantil, for supplying us with the specimens used in this study. We are also grateful to Dr. Burton Polansky for his help with the English revision of the text.

REFERENCES

1. Edwards, J. E.: Functional Pathology of the Pulmonary Vascular Tree in Congenital Cardiac Disease, Circulation **15**:164, 1957.
2. Muller, W.: Die Massenverhaltnisse des menschlichen Herzens, Hamburg and Leipzig, 1883, L. Voss. Referred to by Ziegler.[4]
3. Wideroe, S.: Die Massenverhaltnisse des Herzens unter pathologischen Zustanden, Christiania, 1911, Dybward. Referred to by Ziegler.[4]
4. Ziegler, R. F.: Electrocardiographic Studies in Normal Infants and Children, Springfield, Ill., 1951, Charles C Thomas, Chapter V.
5. Ziegler, R. F.: The Importance of Positive T Waves in the Right Precordial Electrocardiogram During the First Year of Life, AM. HEART J. **52**:533, 1956.

The Evaluation of the Degree of Mitral Insufficiency by Selective Left Ventricular Angiocardiography

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The first successful injection of contrast medium into the left ventricle was made by Nuvoli,[1] in 1936, in a patient with an aortic aneurysm. In 1951, Ponsdomenech and Nuñez[2,3] reported left ventricular angiocardiography in 30 patients, 2 of whom had mitral insufficiency. In 1956, Smith, Wilson, Gregg and Klassen[4,5] found 10 cases of mitral insufficiency in a series of 30 patients who were undergoing left ventricular angiocardiography. They classified the degree of mitral insufficiency according to the degree of opacification of the left atrium.

In cases of mitral insufficiency, selective angiocardiography with contrast injection into the left atrium[6-9] is of value in proving the absence or presence of a concomitant mitral stenosis, and sometimes of an aortic stenosis, and the thickness and mobility of the mitral valves. In this way the relatively rare cases of pure mitral insufficiency with a dilated annulus can be diagnosed and referred for open-heart operation.

The aim of this paper is *to evaluate the degree of the regurgitation through the mitral valves* by the method of contrast injection into the left ventricle.[8] Such evaluation is a very important practical problem, since in cases of combined mitral stenosis and mitral insufficiency a conventional transventricular dilatation of the mitral orifice can be recommended as beneficial only if the regurgitation is slight. On the other hand, when the regurgitation is more pronounced, not much is gained by the closed operation.

At present, we are convinced that cases with pure mitral stenosis will be handled by closed methods, and it is therefore of the greatest importance to establish whether there is a regurgitant component great enough to warrant an open-heart operation with annuloplasty under extracorporeal circulation.

The present paper is based on our experience in 33 patients with mitral insufficiency in a series of 150 left ventricular angiocardiographies.

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METHOD

After premedication of the patient with morphine and scopolamine, a polyethylene catheter was introduced, usually into the left femoral artery, by Seldinger's method.[10] Compression of both common carotid arteries was performed, and the effect on heart rate was recorded by ECG as a test of the compression per se.

The left ventricle was punctured from the apex, according to Brock,[11] under local anesthesia. Left ventricular and femoral arterial pressures were registered simultaneously with electrical manometers (Elema) and recorded by a direct-writing 4-channel oscillograph (Mingograph 42, Elema) in order to detect a pressure gradient over the aortic valves. In the other two channels the ECG and the sequences of the angiocardiographic exposures were recorded (Fig. 1).

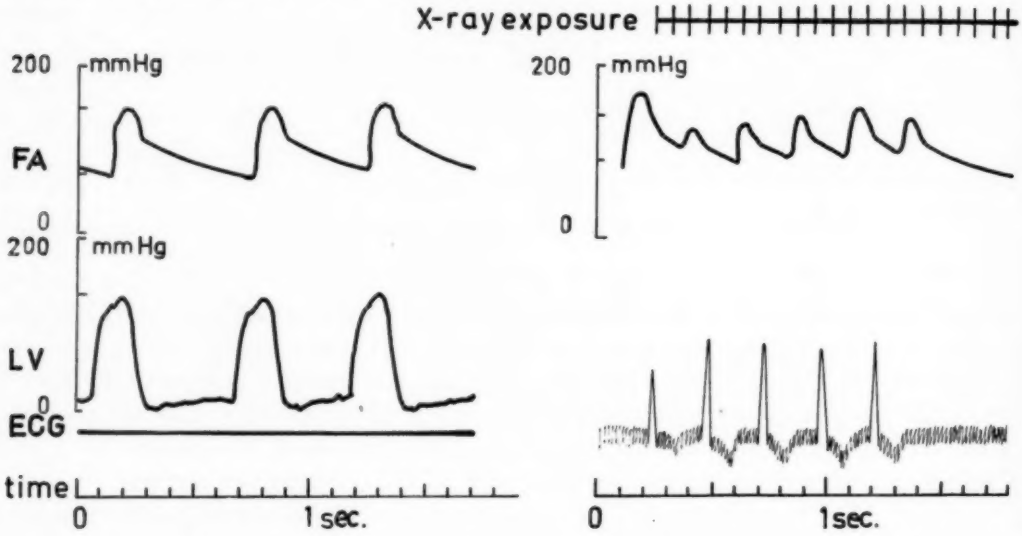

Fig. 1.—X-ray markings, femoral arterial pressure (*FA*), left ventricular pressure (*LV*), and ECG recordings. *To the left:* Before injection of contrast. *To the right:* During injection of contrast. The recordings are those of Case 52, a 33-year-old woman with a heart volume of 820 ml. per square meter of body area. LV = 135/2; FA = 144/75 mm. Hg. During the injection of contrast, 5 ventricular extrasystoles occurred, and the systemic blood pressure decreased from 149/72 before to 144/92 mm. Hg during the injection of contrast.

After measurement of pressure, breathing of oxygen, and observation that the left ventricular curve remained free and undamped when the direction of the needle (of 1.30 mm. internal diameter and 1.55 mm. external diameter) was changed, injection of contrast, 1 ml./Kg. of body weight of 76 per cent Urografin was performed. (Urografin is a water-soluble mixture of methylglucamine and sodium salts of N, N′-diacetyl-3.5-diamino-2, 4, 6-tri-iodobenzoic acid in the proportion of 1 to 6.6.) During this phase of the investigation both common carotid arteries were compressed in order to reduce the flow of contrast to the brain. The speed of injection was 30 ml. per second, and exposures were made in two planes with 6 pictures per second for 4 seconds, followed by 1 to 2 pictures per second for 15 seconds.

After the injection, electrocardiographic and roentgenologic examination of the chest was made. The patient was retained in the Department of Thoracic Surgery during the next 24 hours for close supervision, and measurements of blood pressure and pulse rate were made. Restudies by ECG and x-ray were made on the next day.

Changes in Heart Rate and Rhythm and Systemic Arterial Pressure During Left Ventricular Angiocardiography.—Side effects complained of by the patients often were a feeling of warmth which was followed sometimes by headache immediately after the injection of contrast.

Before the examination, 16 of our 33 patients with mitral insufficiency had sinus rhythm (associated in 2 patients with auricular, and in 2 others with ventricular, extrasystoles); 16 patients had auricular fibrillation (7 of whom had ventricular extrasystoles, too); and the other patient had ectopic nodal rhythm (auricular fibrillation with a complete A-V block). During the series of injections of contrast, from one to seven ventricular extrasystoles usually were present (27 cases). When the injection of contrast was ended, but during the continued exposure to x-ray, bradycardia sometimes developed (12 to 55 beats per minute in 11 cases). Among these cases there were 5 cases of asystole (Cases 13, 20, 33, 47, 52), consisting in the least pronounced case (Case 20) of an interval of 3 seconds between two heart beats, and in the most pronounced case (Case 52) of intervals of 7, 6, 3, and 2 seconds between the following heart beats.* Immediately after the investigation, tachycardia of variable degree developed in 21 patients; the heart rate was usually between 100 and 140, but in 3 patients it was between 160 and 170 beats per minute. The heart rhythm and rate rapidly returned to the same state as before the investigation (see Table II).

In summary, the changes in heart rhythm and rate during the left ventricular angiocardiography consisted in repeated ventricular extrasystoles at a high frequency during the time of injection of contrast. At the end of the injection of contrast, bradycardia developed in 11 cases, in 5 of which there was asystole, and after the investigation a temporary tachycardia was usually present. In no case was any protracted disturbance of the heart rhythm or rate present.

As a result of the above-mentioned heart arrhythmias, some changes in the systemic arterial pressure developed. Before the examination the values recorded ranged from 190/50 to 100/65 mm. Hg, with an average of 150/73 mm. Hg. During the injection of contrast and x-ray examination the same values ranged from 225/75 to 100/50 mm. Hg, with an average of 137/76 mm. Hg. During the continued x-ray examination the values were 175/50 to 80/45 mm. Hg, with an average of 143/48 mm. Hg, and immediately after the examination they were 180/70 to 80/50 mm. Hg, with an average of 118/55 mm. Hg. Thus, the decrease in systolic pressure during the examination was, on an average, less than 10 per cent of the value before the injection of contrast.

The Competent Mitral Valves During Left Ventricular Angiocardiography.— In animal investigations, Paul, Oppenheimer, Lynch and Stauffer[12] proved that a regurgitation through normal mitral valves during left ventricular angiocardiography takes place during asystole, bradycardia, sinus arrhythmia, and compensatory pauses after an extrasystole. Such a regurgitation depends on the presence of a long period of ventricular diastasis. On the other hand, ventricular tachycardia will shorten or eliminate diastasis and prevent a regurgitation through normal valves. The presence or absence of atrial systole did not play any role in regurgitation.

It has been suggested that bradycardia may be produced by the contrast media themselves, and that receptors exist in the left ventricle which cause reflex bradycardia in response to increases in the left ventricular pressure within

*In this paper, asystole is defined as an interval between two heart beats of more than 2 seconds.

physiologic limits. Regurgitation associated with mitral valvular lesions is systolic in time, and thus differs from the false cases.

In human beings, we found no x-ray signs of regurgitation through the mitral valves at the time of left ventricular angiocardiography in 10 patients (with mitral and/or aortic stenosis); these patients were later operated upon and at the time of operation no regurgitation could be palpated. Of these 10 patients, 4 had a period of asystole from 3 to 9 seconds, without any evidence of a regurgitation on the angiocardiograms (see Table I). All patients with asystole had auricular fibrillation before the investigation. The heart rate after the injection varied from 30 to 150 per minute, and most patients had a series of ventricular extrasystoles during the injection of contrast and exposure to x-ray.

TABLE I. CHANGES IN HEART RHYTHM OBSERVED DURING AND AFTER DIRECT INJECTION OF CONTRAST MEDIUM INTO THE LEFT VENTRICLE WITHOUT ANY FALSE REGURGITATION OF CONTRAST MEDIUM BEING OBSERVED AT ANGIOCARDIOGRAPHY. ABSENCE OF REGURGITATION WAS PROVED AT OPERATION

HEART RHYTHM BEFORE INVESTIGATION		CHANGE IN HEART RHYTHM DURING AND IMMEDIATELY AFTER CONTRAST INJECTION INTO THE LEFT VENTRICLE		
AURICULAR FIBRILLATION	SINUS RHYTHM	ASYSTOLE (SEC.)	VENTRICULAR EXTRASYSTOLES	HEART RATE (MIN.)
+		6	−	30
+		4	+	75
+		−	+	140
+		3	+	100
	+	−	+	70–140
	+	−	+	35–100
	+	−	+	80–130
+		−	+	70–150
+		9	−	Bradycardia
+		−	+	

On the other hand, we encountered an asystole of 4 seconds in one patient during ventricular angiocardiography. During this asystole a slight mitral regurgitation was observed on the angiocardiogram, with the left atrium not completely filled with contrast medium. However, the contrast disappeared from the left atrium immediately after the asystole ended. At the time of operation for the combined mitral and aortic stenosis no regurgitation could be palpated at the mitral orifice. Thus, in this case the asystole caused a false impression of mitral regurgitation. However, on the basis of the angiocardiogram, this had already been regarded as a very slight regurgitation because the left atrium was not completely filled, and, of course, the left atrium could not empty during the asystole.

Furthermore, one completely normal heart has been investigated by left ventricular angiocardiography, and no regurgitation of contrast medium into the left atrium was found. In this case there were 5 ventricular extrasystoles during the time of injection of contrast, followed by sinus rhythm which increased in rate from 60 to 100 per minute.

Thus, we have not found that ventricular extrasystoles, bradycardia, or tachycardia in human beings cause a false regurgitation through the mitral valves. Furthermore, asystole does not usually cause a mitral regurgitation in human beings who have mitral stenosis. Of 5 patients with asystole, there was a false regurgitation of contrast medium in only one case during the left ventricular angiocardiography.

We can conclude, therefore, that if no contrast medium is seen regurgitating through the mitral orifice, there can be no significant regurgitation. Furthermore, if the left atrium is filled with contrast in the absence of an asystole, this situation will correspond to a mitral regurgitation.

Difficulties in Assessment of the Presence or Degree of Contrast Opacification of the Heart Chambers During Left Ventricular Angiocardiography.—Small differences in contrast densities may be overlooked. Thus it is very difficult to determine exactly whether a very slight regurgitation is present or whether a heart chamber is empty of contrast. Therefore, all emptying times, whether measured in seconds or in number of ventricular contractions, are not fully exact.

The emptying time of the left atrium and the left ventricle was assessed as the time from the end of the injection to the moment when the actual heart chamber was empty of contrast medium, and the number of ventricular con-

TABLE II. CHANGES IN HEART RHYTHM AND RATE DURING LEFT VENTRICULAR ANGIOCARDIOGRAPHY IN 33 CASES OF MITRAL INSUFFICIENCY

TIME	RHYTHM							INFORMATION LACKING
	SINUS	SINUS + ES	SINUS + vES	A.F.	A.F. + vES	NODAL	1–7 vES	
Before injection	12	2	2	9	7	1	—	–
During injection + x-ray exposure	3	1	–	—	–	–	27	2
During x-ray exposure (continued)	10	3	2	9	7	1	–	1
After x-ray exposure	13	1	1	10	4	1	–	3

TIME	RATE				INFORMATION LACKING
	NORMAL (55-90/MIN.)	TACHYCARDIA (100-170)	BRADYCARDIA (12-55)	ASYSTOLE (OF THOSE WITH BRADYCARDIA)	
Before injection	24	6	2	–	1
During injection + x-ray exposure	7	24	1	–	1
During x-ray exposure (continued)	17	3	11	5	2
After x-ray exposure	7	21	2	–	3

A.F.: Auricular fibrillation. ES: Extrasystoles. vES: Ventricular extrasystoles.

tractions during this time was registered. With few exceptions (see Table V) there was a high degree of correlation between the emptying time in seconds and the number of ventricular contractions during the same time (this ratio was 1.3:1). Occasionally, however, these two indices of mitral regurgitation may give controversial results (see Case 31, below). The number of ventricular contractions is, however, more reliable in assessing the degree of mitral regurgitation than is the left atrial emptying time measured in seconds.

EVALUATION OF DEGREE OF MITRAL INSUFFICIENCY

The degree of mitral insufficiency in 33 cases has been evaluated by left ventricular angiocardiography according to the following principles: degree of contrast filling of the left atrium; left atrial emptying time; comparison of the left atrial and aortic contrast filling.

I. *The Degree of Contrast Filling of the Left Atrium.*—On the basis of the degree of contrast filling of the left atrium, we have tried to divide our cases of mitral insufficiency into two groups. (1) *Cases with incomplete or complete but very thin contrast filling of the left atrium:* We have observed this early sign of regurgitation in 3 patients (Cases 1, 2, 3), and the findings have corresponded to a small regurgitant jet, palpable 1 to 2 fingerbreadths behind the ostium in 2 of these patients who were operated upon. These degrees of mitral insufficiency are considered to be of no significant importance in the decision of making a transventricular dilatation of a mitral stenosis. (2) *Cases with complete, dense contrast filling of the left atrium:* The density of the atrial contrast is, in many cases, equal to that of the left ventricular contrast. In these cases the degree of mitral regurgitation has, however, been evaluated by methods mentioned below.

II. *Evaluation by the Left Atrial Emptying Time.*—The material was divided into three groups. *Group 1:* Cases in which the left atrial emptying time was 10 seconds or more (12 cases). *Group 2:* Cases in which the left atrial emptying time was between 5 and 10 seconds (7 cases). *Group 3:* Cases in which the left atrial emptying time was less than 5 seconds (14 cases).

In the group with the longest left atrial emptying time, i.e., 10 seconds or more, only 3 patients were accepted for operation. In one case (Case 31) there was an aortic stenosis as well as mitral stenosis and mitral insufficiency. The left atrial emptying time was 17 seconds, but bradycardia (25 per minute) was present, and the left atrium was empty of contrast after only 6 ventricular systoles. At the time of operation a regurgitant jet could be palpated 3, but not 4, fingerbreadths behind the mitral ostium; this was interpreted as only a moderate degree of regurgitation. The left ventricular pressure was 277/20 mm. Hg, with a pressure gradient of 89 mm. Hg over the aortic valves. (Femoral arterial pressure was 188 mm. Hg.)

In a second case (Case 18) with an emptying time of 10 seconds, bradycardia (40 per minute), but no asystole, was present, and the contrast medium disappeared from the left atrium after 7 ventricular systoles. There was a dominating aortic stenosis, with a pressure of 210/15 mm. Hg in the left ventricle, but the pressure gradient was only 25 over the aortic leaflets. (Femoral arterial pressure was 185 mm. Hg.)

In a third case (Case 16) with a left atrial emptying time of 11 seconds, there was a combination of mitral stenosis and mitral insufficiency. The heart rate was normal (70 per minute), with 13 ventricular systoles during the left atrial emptying time. There was then a regurgitant jet which could be felt 2, but not 3, fingerbreadths behind the mitral valves. Apart from these cases, only cases with a short emptying time, 1 to 3 seconds, were accepted for operation.

When the material was divided into these three groups, it was found that the patients who had the longest emptying time of the left atrium also had, on an average, the longest circulation time, as well as the biggest hearts and the lowest working capacities. Perhaps the most important correlation was that the patients in the group with the longest atrial emptying time all had auricular fibrillation, but in the group of those with a left atrial time of less than 5 seconds, there were only 3 patients with auricular fibrillation, whereas the other 11 had sinus rhythm (see Table III). Further possible interrelationships were tested and it seemed that in the group with the longest left atrial emptying time there was the highest pulmonary capillary pressure, the highest pulmonary arterial pressure, and the most pronounced apex beat, and in most patients a broad and heaving ictus. There was, however, no interrelationships between the left atrial emptying time and the mobility of the mitral leaflets, calcification in the mitral orifice, or thickness of the left ventricular wall as measured in diastole (see Table IV).

TABLE III. CORRELATION OF LEFT ATRIAL EMPTYING TIME (AS MEASURED IN SECONDS AFTER AN INJECTION OF CONTRAST MEDIUM INTO THE LEFT VENTRICLE) WITH CIRCULATION TIME, HEART RHYTHM, VOLUME, AND WORKING CAPACITY

NUMBER OF CASES	LEFT ATRIAL EMPTYING TIME (SEC.)	CIRCULATION TIME (SEC.)	HEART RHYTHM		VOLUME (ML./M.²)	WORKING CAPACITY
			AURICULAR FIBRILLATION	SINUS RHYTHM		
12	>10	33	12	0	1,050	380
7	10–5	25	1	6	700	450
14	<5	22	3	11	570	530

TABLE IV. CORRELATION OF LEFT ATRIAL EMPTYING TIME (AS MEASURED IN SECONDS AFTER INJECTION OF CONTRAST DIRECTLY INTO THE LEFT VENTRICLE) WITH PULMONARY CAPILLARY PRESSURE (MEAN PRESSURE, MM. Hg), PULMONARY ARTERIAL PRESSURE (SYSTOLIC AT REST, MM. Hg), CALCIFICATION OBSERVED IN TOMOGRAMS, MOBILITY OF MITRAL LEAFLETS, BROAD AND HEAVING APEX BEAT, AND THICKNESS OF VENTRICULAR WALL

NUMBER OF CASES	LEFT ATRIAL EMPTYING TIME (SEC.)	PC (MM. Hg)	PA SYSTOLIC AT REST (MM. Hg)	CALCIFICATION		LEAFLET MOBILITY		BROAD AND HEAVING APEX BEAT		LEFT VENTRICULAR WALL THICKNESS IN DIASTOLE (MM.)
				+	−	GOOD	POOR	+	−	
12	>10	20	45	5	7	4	5	11	1	12
7	10–5	18	27	2	5	–	–	2	5	14
14	<5	14	34	3	8	6	6	7	7	13

Practically an identical emptying time of the left atrium was observed when the injection of contrast medium was made either into the left atrium or into the left ventricle in 5 cases in which both investigations were carried out.

In conclusion, therefore, we can say that the length of the emptying time of the left atrium will reflect primarily whether the heart is in sinus rhythm or in auricular fibrillation. It will then give a general indication of the degree of heart disease, and show a rather good interrelationship of the left atrial emptying time to the heart volume and working capacity, but it cannot be considered as an ideal criterion of the degree of the regurgitation through the mitral orifice.

III. *Evaluation of the Degree of Mitral Regurgitation by Comparison of the Left Atrial and Aortic Contrast Filling.*—In order to compare the proportion of the stroke volume going out into the left atrium with that going out into the aorta, the cases were grouped according to how far through the aorta the contrast volume had reached when the left atrium was completely filled. Naturally, this method cannot be considered exact because the filling of a larger left atrium will take a longer time than the filling of a smaller one. Even the largeness of the left ventricle, the presence of an aortic stenosis and/or insufficiency, as well as the width of the aorta will influence the assessment according to how much of the stroke volume will regurgitate to the left atrium and how much will enter the aorta. Consideration must be given even to extreme bradycardia.

A decreased left ventricular pressure attending frequent premature ventricular contractions must, of course, diminish the mitral regurgitation and the flow of blood out into the aorta alike. Thus, the possible drop in left ventricular pressure may not affect, to any greater extent, the assessment of the angiocardiographic examination.

This method of graduation of a mitral regurgitation has so far been the best one for deciding upon the type of surgical treatment (see Table V).

Group A. Cases for Open Annuloplasty.—When the left atrium has been completely filled before the contrast reaches the top of the aortic arch, we consider that the degree of mitral regurgitation necessitates an open-heart operation. Naturally, a significant aortic insufficiency can cause the same picture with a slow ejection out into the aorta. The combination with an aortic insufficiency must therefore be ruled out by thoracic aortography before the case is classified. Within this group for open-heart operation we found three stages.

Stage 1: The most severe group was that in which the contrast reached only to the root of the aorta when the left atrium was opacified. There were 5 cases in this group. One patient (Case 11), a 29-year-old woman, had a heart volume of 970 ml. per square meter of body area, without any calcification discernible by tomography. The pulmonary capillary pressure was 28, and the systolic pressure in the pulmonary artery was 75 mm. Hg at rest. With the patient under circulatory arrest for 39 minutes, and deep hypothermia of 10.9° C., the lateral commissure was opened and an annuloplasty was made with mattress sutures over Teflon felt. After 4 months of postoperative treatment with a respirator the patient recovered. A second patient (Case 37), a 27-year-old woman, had a heart volume of 1,700 ml. per square meter of body area, a pulmonary capillary pressure of 12, and a systolic pulmonary pressure of 57 mm. Hg at rest (see Fig. 2).

TABLE V

STAGE	CASE NUMBER	SEX	HEART VOLUME (ML./M.²)	CALCIFICATION		RHYTHM	PRESSURES AT REST		ASSOCIATED LESIONS	SURGICAL THERAPY
				MV	AV		PA (SYSTOLIC)	PCV (MEAN)		
1.	7	M	440			Sinus	19	9	AI+MI+MS	Advised open correction
	11	F	970	−	−	Sinus	75	28	MI+MS	Annuloplasty performed
	37	F	1,700	−	−	AF	57	12	MI+AS+MS	Advised open operation
	40	F	630	−	+	Sinus	32	8	AI+VSD+MI	Inoperable because of calcific AI
	53	M	820	−	−	AF	30	20	MI+AI	Advised open correction
2.	12	M	930	−	−	AF	48	32	MI+AI+MS+AS	Advised open correction
	13	F	770	+	−	AF	—	—	MI+MS+AS	Inoperable because of calcification
	19	F	2,400	+	−	AF	65	25	MI+MS	Inoperable because of calcification
3.	21	F	540	+	−	Sinus	20	14	MS+MI+AS+AI	Inoperable because of calcification
	22	F	510	−	−	AF	35	10	MI+AI+MS+AS	Advised open operation
	25	M	750	−	+	Sinus	—	—	AS+MI+AI?	Closed transventricular dilatation
	28	M	550	−	−	Sinus	13	10	AI+MI+AS	Advised open correction
	29	M	1,050	−	−	AF+nodal	100	34	MI+Corrected transposition	Inoperable
	36	M	1,300	−	+	AF	26	13	MI+MS+AS	Inoperable
	46	F	830	−	−	AF	43	22	MI+MS?	Advised open correction
4.	14	M	590	−	−		12	3	AI+MI+MS?	Advised open correction
	16	F	530	−	−	AF	25	16	MS+MI	Closed dilatation
	17	F	650	−	−	AF	40	22	AI+AS+MS+MI	Advised open correction
	18	F	750	−	+	AF	25	12	AS+MS+MI	Closed dilatation
	20	F	530	−	−	Sinus	23	17	MI+AI	Advised open operation
	30	M	490	−	−	Sinus	37	22	MS+AS+MI	Closed correction
	31	M	910	+	+	AF	54	27	AS+MS+MI+AI	Closed dilatation
	43	F	580	−	−	AF	—	35	MS+AS+MI	Closed dilatation
	49	F	630	−	−	AF	22	16	MI+AS+MS+AI	Observation
	52	F	820	−	−	AF	32	11	MI+MS	Advised open operation
5.	1	M	450	+	−	Sinus	Normal	15	MS+MI	Closed dilatation
	2	F	750	−	−	Sinus	80	24	MS+AS+MI+AI	Closed dilatation
	3	M	440	−	−	Sinus	14	4	AI+MI	Observation
	10	M	530	−	+	Sinus	—	—	AS+MI	Closed operation
	33	F	650	−	−	AF	26	20	MS+AS+MI	Closed operation
	34	M	550	−	−	Sinus	25	9	AI+AS+MI	Observation
	35	M	660	−	+	Sinus	37	8	AS+MI+MS+AI	Observation
	47	M	720	−	−	Sinus	71	32	AS+AI+MI	Open correction

AV: Aortic valves. MV: Mitral valves. AF: Auricular fibrillation. MI: Mitral insufficiency. MS: Mitral stenosis. AI: Aortic insufficiency. AS: Aortic stenosis. VSD: Ventricular septal defect. The pressures are given in mm. Hg.

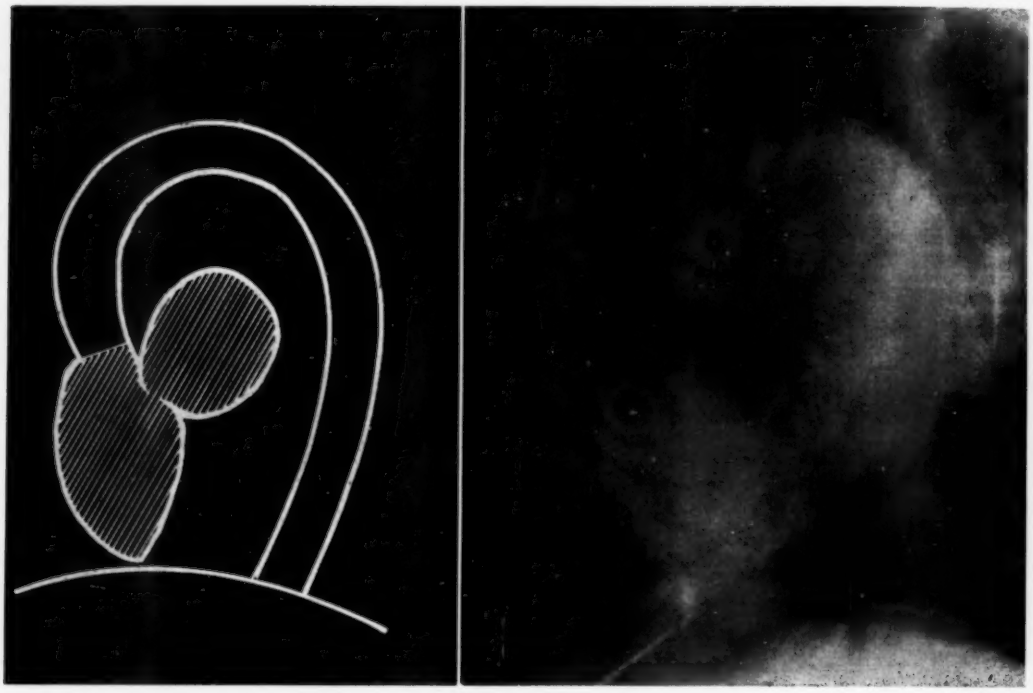

Fig. 2.—Group A, Stage 1. The left atrium was completely filled before the contrast reached the root of the aorta. *Left:* Schematic drawing. *Right:* Left ventricular angiocardiogram. Case 37, a 27-year-old woman with a heart volume of 1,700 ml. per square meter of body area. PA = 57 systolic; PC = 12; LV = 135/8; FA = 140/75 mm. Hg.

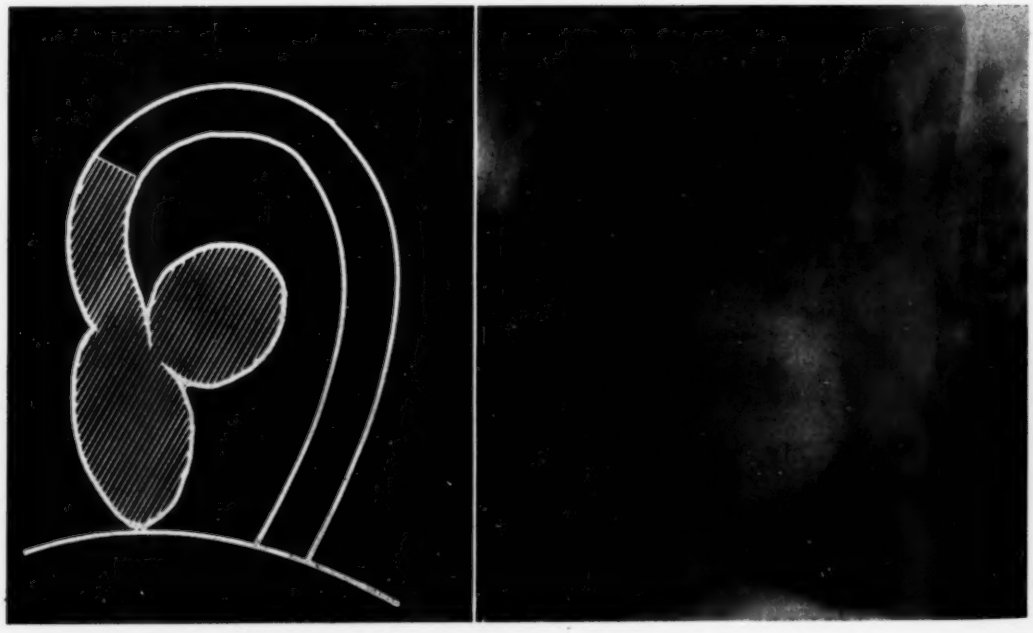

Fig. 3.—Group A, Stage 2. The left atrium was completely filled when the contrast reached halfway up the ascending aorta. *Left:* Schematic drawing. *Right:* Left ventricular angiocardiogram. A 37-year-old woman with a heart volume of 790 ml. per square meter of body area. PA = 50 systolic; PC = 14; LV = 160/0-10; FA = 170/70 mm. Hg. (This case was not included in the material of this report.)

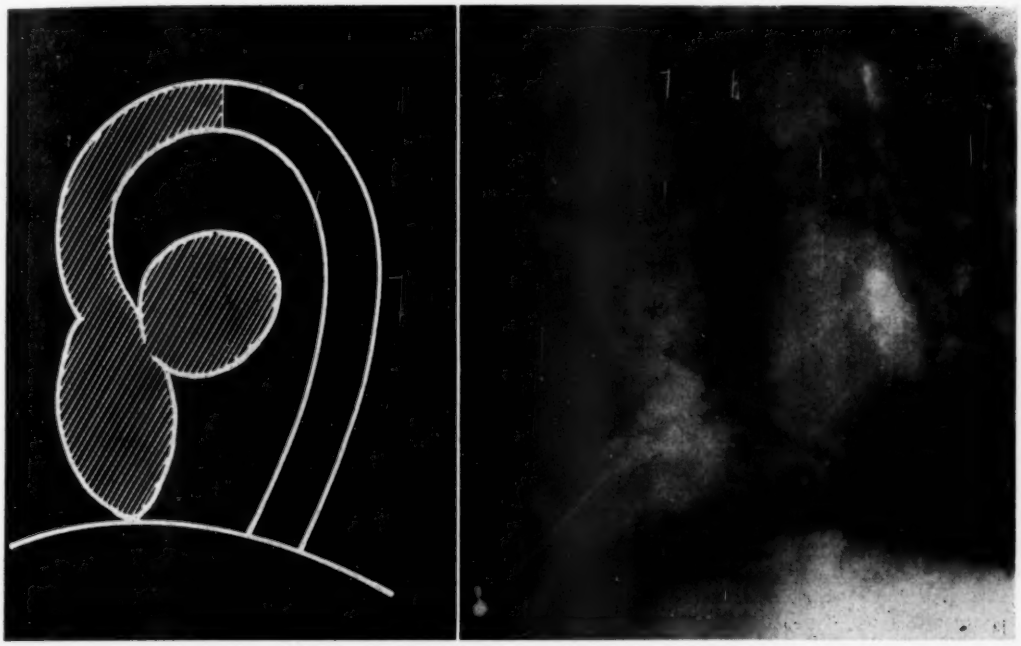

Fig. 4.—Group A, Stage 3. The left atrium was completely filled when the contrast reached the top of the aortic arch. *Left:* Schematic drawing. *Right:* Left ventricular angiocardiogram. Case 21, a 40-year-old woman with a heart volume of 540 ml. per square meter of body area. PA = 20 systolic; PC = 14; LV = 130/0; FA = 135/73 mm. Hg.

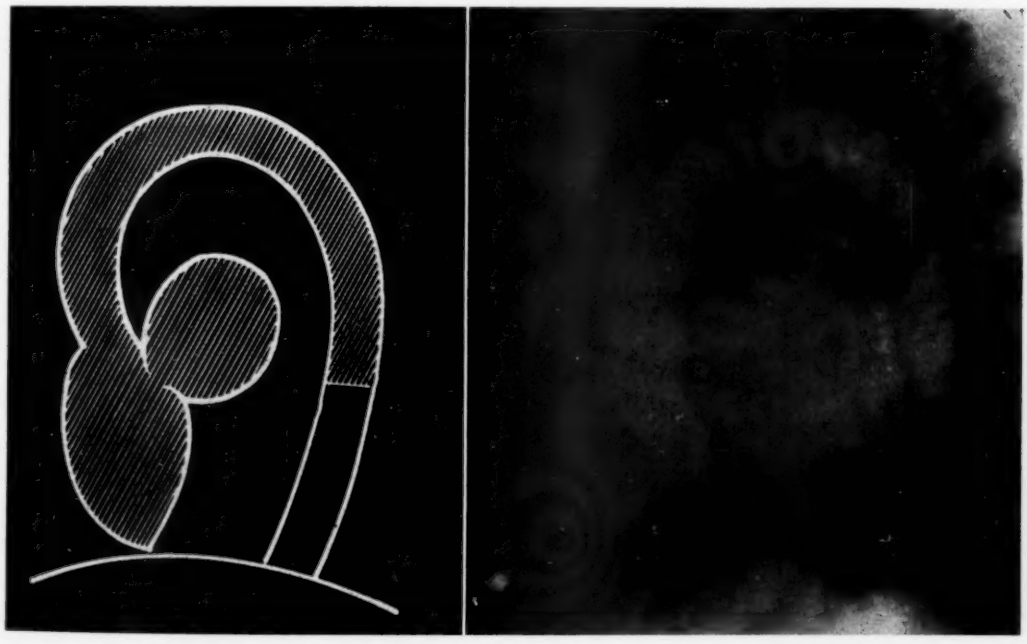

Fig. 5.—Group B, Stage 4. The left atrium was completely filled when the contrast reached halfway down the descending aorta. *Left:* Schematic drawing. *Right:* Left ventricular angiocardiogram. Case 16, a 43-year-old woman with a heart volume of 530 ml. per square meter of body area. PA = 25 systolic; PC = 16; LV = 150/15; FA = 150/75 mm. Hg.

An open-heart operation was advised. Three other patients (Cases 7, 40, and 53) were excluded because of severe aortic insufficiency: both the left ventricle and atrium were opacified after injection of contrast into the ascending aorta. In those cases there was a fluctuation of contrast between the aorta and the left ventricle for 5, 6, and 13 seconds, respectively.

Stage 2: In these cases the contrast reached halfway up the ascending aorta when the left atrium was opacified (see Fig. 3). There were 3 patients (Cases 12, 13 and 19) in this group, and all had big hearts: 770, 930, and 2,400 ml. per square meter of body area. The pulmonary capillary pressure was between 25 and 32, and the pulmonary arterial pressure was between 48 and 65 mm. Hg systolic. Only one patient (Case 12) was advised to undergo an open-heart operation; there were significant calcifications in the other two patients.

Stage 3: In these cases the contrast reached the top of the aorta when the left atrium was opacified. There were 7 patients in this group (see Fig. 4). Only 2 (Cases 22 and 46) were advised to undergo open annuloplasty. Three other patients were considered to be inoperable because of calcifications (Cases 21 and 36) and a concomitant corrected transposition[12] with irreversible changes in the lungs.[29] One patient was excluded because of aortic insufficiency (Case 28); in another (Case 25) who was operated upon for an aortic stenosis with a pressure gradient of 102 mm. Hg over the aortic orifice, the mitral orifice was not palpated.

Group B. Cases for Open or Closed Operation.—

Stage 4: In the 10 patients in this group the contrast reached halfway down the descending aorta when the left atrium was opacified. This is a borderline group, and more experience has to be accumulated before a definite opinion can be expressed. Two patients were recommended for an open-heart operation (Cases 20 and 52). Three patients were operated upon by a closed transventricular dilatation. In those a regurgitant jet was palpable at 4, 3, and 1 cm. behind the mitral orifice, respectively. A satisfactory result was obtained in 2 patients (Cases 43 and 30), but not much was gained in another (Case 16) (see Fig. 5). Three cases were complicated by aortic insufficiency (Cases 14, 17, and 49) and 2 by aortic stenosis (Cases 31 and 18).

Group C. Cases for Closed Transventricular Dilatation.—

Stage 5: In this group the whole of the thoracic aorta filled when the left atrium was opacified. Of the 8 cases in this group the mitral orifice was palpated in 4 cases, with a regurgitant jet 3 cm. (Case 1), 2 cm. (Cases 2 and 10), and no regurgitation in one case (Case 33) palpated in hypotensive anesthesia. An aortic stenosis dominated in 3 cases (Cases 2, 10, and 35), with pressure gradients of 40, 105, and 50 mm. Hg over the aortic ostia. An aortic insufficiency was the dominating lesion in 3 other cases (Cases 3, 34, and 47). In one of these the aortic insufficiency was due to a perforation in one of the bicuspid aortic cusps (Case 47). The pressure in the left ventricle was 194/32 mm. Hg, and the pulmonary capillary pressure was 32 mm. Hg. The anatomy of the mitral orifice was found to be normal at autopsy, and the mitral insufficiency was ascribed to the left heart failure.

In conclusion, therefore, it can be considered that in the cases of the combined mitral insufficiency and mitral stenosis, in which no aortic valvular disease was present, only cases belonging to Groups B and C were accepted for a transventricular dilatation. The value of this operation in the cases of Group B is doubtful. Anyway, we are completely convinced that in the cases of Group A, no closed operation should be performed on the mitral valves.

COMMENT

In all of our 33 cases, mitral insufficiency was associated with other types of valvular lesions. One case was combined with corrected transposition of the great vessels.[13] As may be seen from Table V, the concomitant valvular lesions in 23 cases were mitral stenosis, in 20 cases aortic stenosis, in 17 cases aortic insufficiency, and in 1 case ventricular septal defect. In 11 cases, two types of valvular lesions were present, in 15 cases three types, and in 7 cases four types of valvular heart disease.

Mitral insufficiency was the dominating lesion in 13 cases; it was judged to be of secondary hemodynamic importance in 10 cases, of third degree of importance in 9 cases, and least important in 1 case.

The usual clinical investigations, including right-sided heart catheterization, have been the bases of our diagnostic work. We have found that a comparison of the left atrial and aortic contrast filling after left ventricular injection is the most reliable method for determining the degree of regurgitation through the mitral orifice. In this way the proportion of the stroke volume going out into the left atrium, as compared to the part going out into the aorta, has been evaluated. In many cases, thoracic aortography was performed in order to diagnose or exclude aortic insufficiency.

The accuracy of our assessment of the degree of regurgitation through the mitral orifice has been confirmed at operation in 13 cases. The surgical findings in all cases have showed good agreement with our preoperative evaluation.

Thus, left ventricular angiocardiography has been of great practical value in choosing the adequate type of surgical intervention as well as in determining whether the valvular lesions present are inoperable. *No complication of the investigation* was encountered in this series of 33 cases of mitral insufficiency.

SUMMARY

The evaluation of the degree of the regurgitation through the mitral orifice by comparison of the left atrial and aortic contrast filling after the injection of contrast into the left ventricle is considered to be the best method available. Five stages with regard to how far the contrast has passed into the aorta when the left atrium is completely filled with contrast have been established. The findings at operation in 13 cases were in agreement with our evaluations. We are convinced that in cases in which the left atrium is completely filled when the contrast has reached only the top of the aortic arch, or not that far, no closed operation should be performed on the mitral valves.

REFERENCES

1. Nuvoli, I.: Policlinico, Sez. prat. **43**:227, 1936. Cited by Brock.[11]
2. Ponsdomenech, E. R., and Nuñez, V. B : Heart Puncture in Man for Diodrast Visualization of the Ventricular Chambers and Great Arteries, AM. HEART J. **41**:643, 1951.
3. Nuñez, V. B., and Ponsdomenech, E. R.: Heart Puncture. II. Clinical and Electrocardiographic Results, AM. HEART J. **41**:855, 1951.
4. Smith, P. W., Wilson, C. W., Gregg, H. A., and Klassen, K. P.: Cardioangiography, J. Thoracic Surg. **28**:273, 1954.
5. Smith, P. W., Gregg, H. A., and Klassen, K. P.: Diagnosis of Mitral Regurgitation by Cardioangiography, Circulation **14**:847, 1956.
6. Björk, V. O.: Direct Pressure Measurement in the Left Atrium, the Left Ventricle and the Aorta, Acta chir. scandinav. **107**:466, 1954.
7. Björk, V. O., Kjellberg, S. R., Malmström, G., and Rudhe, U.: The Diagnosis of Mitral Insufficiency, AM. HEART J. **49**:719, 1955.
8. Björk, V. O., and Lodin, H.: Left Heart Catheterization With Selective Left Atrial and Ventricular Angiocardiography in the Diagnosis of Mitral and Aortic Valvular Disease, Prog. Cardiovas. Dis. **2**:116, 1959.
9. Björk, V. O., Kjellberg, S. R., Malmström, G., Nordenström, B., and Rudhe, U.: Cardioangiographic Study of the Mitral and Aortic Valves, Acta radiol. (In press.)
10. Seldinger, S. I.: Catheter Replacement of the Needle in Percutaneous Arteriography, Acta radiol. **39**:368, 1953.
11. Brock, R., Milstein, B. B., and Roos, D. N.: Percutaneous Left Ventricular Puncture in the Assessment of Aortic Stenosis, Thorax **11**:163, 1956.
12. Paul, R. E., Oppenheimer, M. J., Lynch, P. R., and Stauffer, A. M.: Regurgitation of Radiopaque Contrast Material Through Normal Mitral Valves in Cinefluoroscopic Studies of Dogs, J. Appl. Physiol. **12**:98, 1958.
13. Malers, E., Björk, V. O., Cullhed, I., and Lodin, H.: Transposition Functionally Totally Corrected, Associated With "Mitral" Insufficiency, AM. HEART J. **59**:816, 1960.

Electrocardiographic Analysis of Pure Mitral Valvular Disease: A Study Based on Fifty-Seven Cases With Open-Heart Operation

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Evaluations of correlations between electrocardiographic findings and cardiac anatomy and physiology in health and disease are often fraught with difficulties imposed by multiple variables. Frequently, reliance is placed on indirect means, such as clinical impressions, rather than on direct means, such as anatomic observations through postmortem or surgical findings. The use of open-heart operation,[1] however, in conjunction with clinical and cardiac catheterization findings have permitted direct access to exact knowledge of the anatomic as well as dynamic status of the living heart. In this study, the unequivocal data obtained by these anatomic and physiologic explorations have been the basis of a correlation of electrocardiograms with specific lesions, and the significance of the associations have been corroborated by the use of statistical methods. The main objectives of this paper are to determine the electrocardiographic characteristics of pure mitral valvular disease and the differentiations between the specific lesions of pure mitral stenosis, pure mitral insufficiency, and the combined lesion of mitral stenosis and insufficiency.

MATERIAL AND METHODS

The cases of 57 patients with "pure" mitral valvular disease (unassociated with any other cardiac lesion) who underwent open-heart operation in St. Vincent Charity Hospital were reviewed. Of these, 24 patients had pure mitral stenosis, 15 had pure mitral insufficiency, and 18 had combined lesions (mitral stenosis and insufficiency). Diagnosis was based mainly on dyanmic as well as anatomic observations made during open-heart operation, in addition to preoperative clinical and cardiac catheterization findings.

The data included the age, the right ventricular systolic pressure (obtained by routine preoperative cardiac catheterization[2]), and an analysis of the electrocardiogram taken just prior to operation in each patient.

Electrocardiographic analysis included the determination of the following: (1) predominant rhythm; (2) mean electrical axis of the P wave, in degrees, in both the frontal and horizontal

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planes; (3) P-wave duration, in seconds; (4) presence of notching of the P wave (bifid P wave) in either the bipolar limb leads or in the left-sided chest leads (V_4, V_5, or V_6); (5) Macruz index (duration of the P wave divided by duration of the P-R segment[3]); (6) mean electrical axis of the QRS wave, in degrees, in both the frontal and horizontal planes; (7) QRS duration, in seconds; (8) morphologic pattern of the QRS wave in Lead V_1; (9) height of the R wave in Leads V_1 and V_6, in millimeters; (10) height of the S wave in Leads V_1 and V_6, in millimeters; (11) sum of the heights of the R wave in Lead V_6 and the S wave in Lead V_1, in millimeters; (12) ventricular activation time (time of onset of the intrinsicoid deflection[4]), in seconds, of the right and left ventricles; (13) presence of right ventricular hypertrophy; and (14) presence of left ventricular hypertrophy.

Calculation of the mean electrical axis was made by using Ashman units[5] plotted against the triaxial reference system of Bayley[5] for the frontal plane. In the horizontal plane, the mean electrical axis of the P wave was calculated by using Lead V_6 as the lateral parietal projection (0°), and Lead V_1 as the anterior parietal projection (+90°), of the "electrical center" of the atria, as indicated by Peñaloza and Tranchesi.[6] For the mean electrical axis of the QRS wave in this plane, Lead V_6 was used as the lateral parietal projection (0°), and Lead V_2 as the anterior parietal projection (+90°), of the "electrical center" of the ventricles, as had been employed by Tranchesi.[7]

The mean and the corresponding standard deviation (S. D.) of each item under study under each type of valvular lesion were computed. Comparisons were made between the different types of valvular lesions in order to determine any significant difference by means of standard statistical methods.[8] Prevalence was calculated in per cent. All measurements were made with the aid of a magnifying glass, electrocardiographic calipers, and standard electrocardiographic rulers.

RESULTS

Age.—The age of the patients ranged from 12 to 56 years. The mean age of those with pure mitral stenosis was 42.9, ranging from 21 to 53; the mean age of those with pure mitral insufficiency was 34.2, ranging from 12 to 53; the mean age of those with combined lesions was 38.8, ranging from 16 to 56.

Right Ventricular Pressure.—The mean value of the right ventricular pressures in the group which had pure mitral stenosis was 61.0 ± 25 mm. Hg, whereas in the group with pure mitral insufficiency, the mean was 42.1 ± 12.1 mm. Hg. In the group which had combined lesions, the mean was 50.0 ± 15.5 mm. Hg.

Electrocardiographic Findings.—Table I shows a summary of the electrocardiographic findings in the different types of mitral valvular lesions.

1. *Rhythm:* Of the 57 patients, 24 (42.1 per cent) had sinus rhythm, and the rest (58.9 per cent) had atrial fibrillation. Prevalence of the latter was higher in the patients with mitral insufficiency (73.3 per cent) and in those with combined lesions (61.1 per cent) than in those with mitral stenosis (45.8 per cent). Statistically, differences were not highly significant ($p > .05$).

2. *Mean electrical axis of the P wave ($S\hat{A}P$):* No significant difference could be determined between the mean values of the mean electrical axes in both the frontal and horizontal planes in the different types of lesions. In the frontal plane, the mean values of $S\hat{A}P$ were oriented inferiorly and to the left, whereas in the horizontal plane, they were oriented to the left and backward. There is considerable scatter noted in both the frontal and horizontal planes (values for the S.D. ranged from 20 to +100 per cent of the mean values).

3. *Duration of the P wave:* The mean values of the duration of the P wave in all three types of lesions were greater than 0.10 sec., and showed no significant differences. Single measurements ranged from 0.09 (1 case only) to 0.16 sec.

4. *Presence of notching of the P wave (in cases of sinus rhythm):* Notching of the P wave was present in 91.6 per cent of all of the cases, in 84.62 per cent of the cases of mitral stenosis, in 100 per cent of the cases of mitral insufficiency, and in 100 per cent of the cases of the combined lesions.

5. *Macruz index:* The Macruz index ranged from 1.0 to 4.3, with means greater than 2.0 for all three types of lesions.

6. *Mean electrical axis of the QRS wave (SÂQRS):* In the frontal plane, there were near mean values of the mean electrical axis for all three types of valvular lesions; all were oriented inferiorly within Sextant V of Bayley.[5] Considerable overlapping in the frequency distribution of the mean electrical axis was noted between the different lesions, as is shown in Fig. 1. A poor correlation (correlation coefficient [r] .31) was obtained by plotting this datum to right ventricular systolic pressure (see Fig. 2).

In the horizontal plane, the SÂQRS ranged from $-57°$ to $+135°$ in cases of mitral stenosis, from $-67.5°$ to $0°$ in cases of mitral insufficiency, and from $-67.5°$ to $+60°$ in cases of combined lesions. There were 4 cases in which the mean electrical axis was greater than $0°$ in this plane (3 cases of pure mitral stenosis and 1 case of combined lesions), ranging from $+22.5°$ to $+135°$. In the computation of the mean values, only those cases in which the mean axes were oriented posteriorly were included (94.73 per cent of the whole series), in order to obviate the effects of skewness of the frequency distribution of this datum in cases of mitral stenosis and combined lesions. This done, no significant differences in the mean values of the three kinds of lesions were noted. Fig. 3 shows the frequency distribution in the three types of lesions in this plane.

By correlation to right ventricular systolic pressure, in all cases in which the mean electrical axis was oriented anteriorly the pressures ranged from 80 to 125 mm. Hg.

7. *Duration of the QRS wave:* Duration of the QRS wave ranged from 0.06 to 0.11 second, with a mean of 0.078 second for the whole group. Its mean values between the different types do not differ significantly.

8. *Morphology of the QRS wave in Lead V_1:* Six different kinds of QRS configurations were noted in Lead V_1: rS, rSr′, QS, Rs, qR, and rsR′. The rS type was predominant in all, with an incidence of 63.15 per cent for the whole group. The rSr′, when present, was predominant in cases of mitral stenosis, as compared to cases of mitral insufficiency (25.0 versus 6.6 per cent), but statistically was insignificant ($p > .05$).

Hemodynamically, cases with an rSr′ type of morphology showed right ventricular systolic pressures that ranged from 32 to 110 mm. Hg, with a mean of 53.7 ± 23.0 mm. Hg. Those with a qR, Rs, or rSR′ type of morphology, however, showed right ventricular systolic pressures that ranged from 80 to 125 mm. Hg, with a mean of 97.5 ± 16.7 mm. Hg.

9a. *Height of R wave in Lead V_1 (VR_1):* No significant differences were established between the means in the three groups of cases. Measurements ranged from 0.5 to 8.0 mm. in cases of mitral stenosis, 0 to 5.5 mm. in cases of mitral insufficiency, and 0 to 9.0 mm. in cases of combined lesions.

9b. *Height of R wave in Lead V_6 (VR_6):* In cases of mitral stenosis the height of the R wave in Lead V_6 ranged from 4 to 22.0 mm., with a mean of 10.21 ± 4.30 mm. Statistically, this differed very significantly from the findings in cases of mitral insufficiency, in which the R wave ranged from 15.0 to 35.0 mm., with a mean of 22.46 ± 7.01 mm. ($p < .001$). In cases of combined lesions the range was 8.0 to 28.0 mm., with a mean of 13.86 ± 5.2 mm. Compared to the findings in cases of mitral insufficiency, the difference is also statistically significant ($p < .001$). Compared to the findings in the cases of mitral stenosis, the difference between the means showed a p value $< .025$.

TABLE I

	ANATOMIC DIAGNOSIS		
	PURE MITRAL STENOSIS	PURE MITRAL INSUFFICIENCY	COMBINED LESIONS
Rhythm (incidence in number of cases):			
Sinus	13	4	7
Atrial fibrillation	11	11	11
The P Wave:			
Mean electrical axis (mean values in degrees)			
Frontal plane	+44.2 ± 22.0	+40.0 ± 18.0	+56.4 ± 11.0
Horizontal plane	−18.0 ± 13.0	−7.0 ± 18.0	−9.0 ± 14.0
Duration (mean values in seconds)	0.118 ± 0.020	0.135 ± 0.021	0.118 ± 0.020
Presence of notching (incidence in number of cases)	11	4	7
Macruz index (mean values)	2.40 ± .31	3.25 ± .40	2.53 ± .40
The QRS Wave:			
Mean electrical axis (mean values in degrees)			
Frontal plane	+77.5 ± 33.0	+68.0 ± 29.1	+69.4 ± 25.0
Horizontal plane	−36.8 ± 21.2	−41.1 ± 17.3	−45.5 ± 18.2
Duration (mean values in seconds)	0.075 ± 0.010	0.081 ± 0.021	0.076 ± 0.013
Morphology in Lead V_1 (incidence in number of cases)			
rS	15	11	12
rSr′	6	1	3
QS	0	3	2
Rs	1	0	0
qR	2	0	0
rsR′	0	0	1
Height of R wave (mean values in mm.)			
V_1	2.43 ± 1.80	1.60 ± 1.60	1.48 ± 1.80
V_6	10.21 ± 4.30	22.46 ± 7.01	13.86 ± 5.20
Height of S wave (mean values in mm.)			
V_1	5.50 ± 3.69	10.43 ± 6.20	5.61 ± 3.60
V_6	1.47 ± 2.70	—	1.53 ± 2.60
$VR_6 + VS_1$ (mean values in mm.)	15.67 ± 5.04	32.90 ± 10.38	19.47 ± 6.38
Ventricular activation time (mean values in seconds)			
V_1	0.026 ± 0.010	0.021 ± 0.002	0.031 ± 0.002
V_6	0.038 ± 0.008	0.056 ± 0.004	0.044 ± 0.003

10a. *Height of the S wave in Lead V_1 (VS_1):* The height of the S wave in Lead V_1 ranged from 0 to 13.0 mm. in cases of mitral stenosis, with a mean of 5.50 ± 3.69 mm.; from 2 to 22.5 mm. in cases of mitral insufficiency, with a mean of 10.43 ± 6.20 mm.; and from 0 to 13.5 mm. in cases of combined lesions, with a mean of 5.61 ± 3.60 mm. When the cases of mitral stenosis were compared to the cases of mitral insufficiency, the difference between means showed a p value < .005; between the cases of mitral insufficiency and those of the combined lesions, the p value was < .02; and between cases of mitral stenosis and cases of combined lesions, the p value was > .05.

10b. *Height of S wave in Lead V_6 (VS_6):* No significant differences between the means were established. It should be noted that in the group with mitral insufficiency, only 1 case showed a measurable S wave (0.5 mm.).

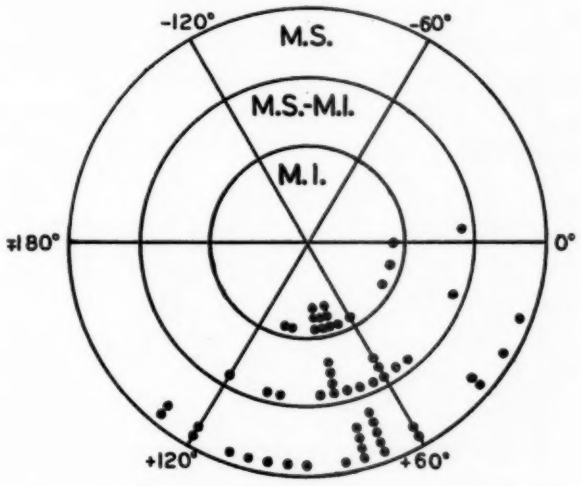

Fig. 1.—Frequency distribution of the SÂQRS in the frontal plane in cases of pure mitral insufficiency (*M.I.*), mitral stenosis and insufficiency (*M.S.-M.I.*), and pure mitral stenosis (*M.S.*).

11. *VR_6 plus VS_1:* In cases of mitral stenosis, the sum of the R in Lead V_6 plus the S in Lead V_1 ranged from 6.0 to 24.5 mm.; and in cases of mitral insufficiency, it ranged from 18.0 to 55.5 mm.; and in cases of combined lesions, the range was from 9.0 to 32.0 mm. The difference between means in cases of mitral stenosis (15.67 ± 5.04 mm.) and cases of mitral insufficiency (32.90 ± 10.38 mm.) showed a p value < .001. Between cases of mitral insufficiency and cases of combined lesions, the p value was also < .001. Between cases of mitral stenosis and cases of combined lesions, the p value was < .05. In cases of mitral insufficiency with sinus rhythm the mean of $VR_6 + VS_1$ was 41.75 ± 10.4 mm., and with atrial fibrillation the mean was 29.68 ± 8.3 mm.

12. *Ventricular activation time:* When Lead V_1 was used to measure the ventricular activation time of the right ventricle, no significant differences between the means of the different valvular lesions were established. In regard to the left ventricle (when Lead V_6 was used) the mean ventricular activation time in cases of mitral stenosis was 0.038 ± 0.008 second, as compared to 0.056 ± 0.004

second in cases of mitral insufficiency; the difference between the means showed a p value < .001. The same held true when cases of mitral insufficiency were compared to cases of combined lesions which had a mean of 0.044 ± 0.003 second. Between cases of mitral stenosis and cases of combined lesions the p was < .025.

13. *Presence of right ventricular hypertrophy:* Electrocardiographic changes diagnostic of right ventricular hypertrophy (Myers' criteria[9]) were present in 4 cases only—3 cases of mitral stenosis and 1 case of combined lesions.

14. *Presence of left ventricular hypertrophy:* Precordial electrocardiographic changes characteristic and diagnostic of left ventricular hypertrophy (Sokolow and Lyon's criteria[10]) were present in 6 patients, all with mitral insufficiency (40 per cent incidence in patients with this lesion).

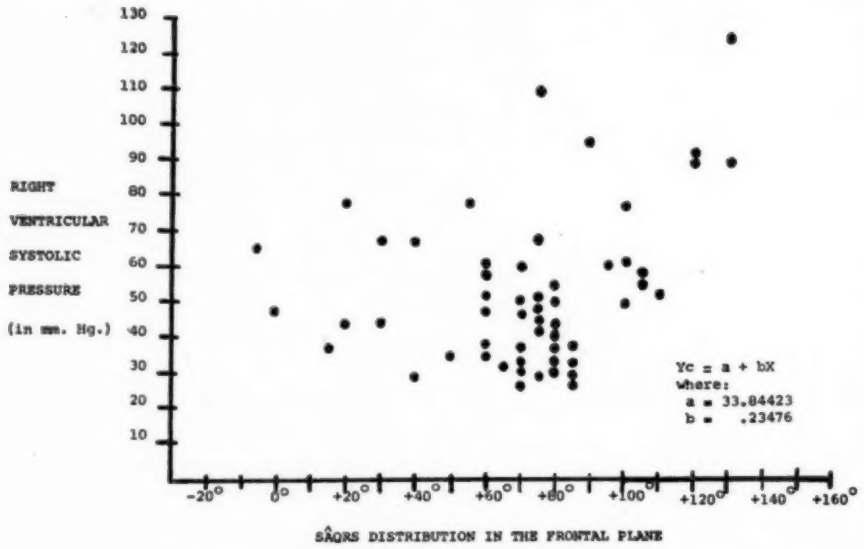

Fig. 2.—Relationship of SÂQRS of mitral valvular disease in the frontal plane to right ventricular systolic pressure. The coefficient of correlation [r] is .31.

COMMENTS

This study demonstrates that electrocardiographic findings in pure mitral valvular disease have certain characteristics in common, as well as identifying patterns of specific lesions.

Rhythm.—Atrial fibrillation was more common than sinus rhythm in the series as a whole. Between specific lesions, the prevalence of atrial fibrillation was greater in cases of pure insufficiency and cases of combined lesions than in cases of pure stenosis. This finding agrees with reports of other authors[11,12]; however, statistically, differences in prevalences of atrial fibrillation in cases with different lesions were not highly significant in this series.

Left Atrial Enlargement.—Abnormal P waves, indicative of left atrial enlargement, were found in all cases with sinus rhythm. The most consistent electrocardiographic findings expressive of left atrial enlargement were prolonged duration of the P wave (> 0.10 second), notching or bifid P waves, and Macruz

indices[3] greater than 1.6. Averages of the mean electrical axis of the P wave in the frontal plane did not differ greatly from reported normal values.[13] The frequency distribution of this datum showed a large degree of scatter, indicating that it is a poor criterion of atrial enlargement.

Orientation of the SÂQRS.—In all three types of lesions, the mean values of the SÂQRS in the frontal plane were oriented in Sextant V of Bayley, and did not vary more than 10 degrees from each other (Fig. 4). Since this is a finding in common among the different lesions, it is best attributed to some common cause. The low correlation between right ventricular systolic pressure and the rightward shift of SÂQRS (Fig. 2) does not support the view[14] that right axis deviation is attributable to right ventricular overloading. The more probable cause is rotation clockwise along the anteroposterior and/or longitudinal axes, consequent to left atrial enlargement, which is a condition common to the three types of mitral disease.

Mean values (4 cases omitted) of the distribution of SÂQRS in the horizontal plane were oriented backward and did not vary significantly from each other, irrespective of the type of lesion. In the 4 cases (3 cases of mitral stenosis and 1 case of combined lesions) in which SÂQRS was oriented anteriorly, there was severe right ventricular overloading.

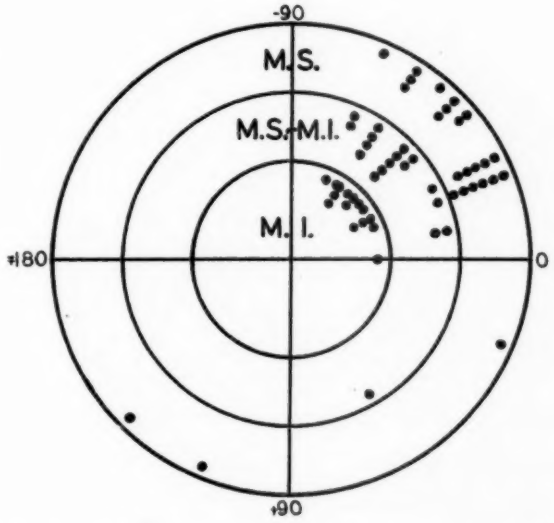

Fig. 3.—Frequency distribution of SÂQRS in the horizontal plane in cases of pure mitral insufficiency (*M.I.*), mitral stenosis and insufficiency (*M.S.–M.I.*), and pure mitral stenosis (*M.S.*).

Morphology of the QRS in Lead V_1.—A prominent R wave in Lead V_1, manifested as Rs, qR, or rsR′, was found in only 3 cases of mitral stenosis and in 1 case of combined lesions, in all of which there was severe right ventricular overloading.

The rSr′ configuration was more common in cases of mitral stenosis than in cases of insufficiency or combined lesions; statistically, this difference in prevalence was not highly significant. As has been observed,[15] this wave form is not associated with any definite span of pressure levels.

Presence of Ventricular Hypertrophy.—Electrocardiographic differentiation between mitral stenosis and mitral insufficiency would be easy if all cases of mitral stenosis showed classic electrocardiographic signs of right ventricular hypertrophy, and all cases of mitral insufficiency showed signs typical of left ventricular hypertrophy. But such is not the case. To complicate matters, reported prevalences[12,16-22] of right and left ventricular hypertrophy are as variable as the criteria used in making these diagnoses. In this study, there were only 4 patients (7 per cent of the whole series) who manifested electrocardiographic signs diagnostic of right ventricular hypertrophy,[9] and 6 (10.5 per cent) who showed definite evidence of left ventricular hypertrophy[10] in precordial leads. The 4 patients with right ventricular hypertrophy were those whose SÂQRS were oriented anteriorly in the horizontal plane, and whose QRS in Lead V_1 showed prominent R waves. The patients who manifested signs of left ventricular hypertrophy all had pure mitral insufficiency; these represent a 40 per cent prevalence in this lesion.

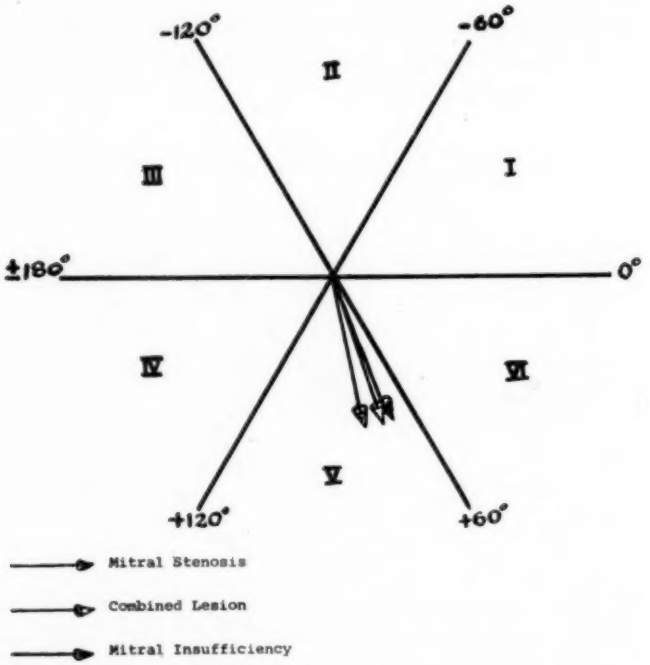

Fig. 4.—Orientation in the frontal plane (subdivided into the sextants of Bayley) of the means of SÂQRS in cases of pure mitral stenosis, pure mitral insufficiency, and the combined lesion of mitral stenosis and insufficiency.

Magnitude of VR_6 and VS_1.—When deflections of the QRS wave in Leads V_1 and V_6 were measured, significant differences were found in the means of VR_6 and VS_1 between the different lesions. The mean VR_6 in cases of mitral insufficiency (22.46 ± 7.01 mm.) varied significantly from that in cases of mitral stenosis (10.21 ± 4.30 mm.) and in cases of the combined lesions (13.86 ± 5.20 mm.). Similarly, the means of VS_1 in cases of mitral stenosis and cases of mitral insufficiency differed significantly (10.43 ± 6.20 mm. compared to 5.50 ± 3.69

mm., respectively). The significance of this differentiation is enhanced when VR_6 plus VS_1 was measured; for cases of mitral insufficiency this mean was 32.90 ± 10.38 mm., whereas for cases of mitral stenosis it was 15.67 ± 5.04 mm., and for cases of the combined lesions the mean was 19.47 ± 6.38 mm. These measurements showed no significant differences (when a p value $< .01$ was used as the level for significance) between means in cases of mitral stenosis and in cases of combined lesions.

The means observed in this study of VR_6 plus VS_1 for cases of mitral insufficiency are similar to those reported by Bateman and January[23] and those described by Wierum and Glenn,[24] in cases of mitral insufficiency associated with atrial fibrillation. The latter is in contrast to findings in this study which showed a higher mean of VR_6 plus VS_1 in cases of mitral insufficiency with sinus rhythm than with atrial fibrillation.

Activation Time of Left Ventricle.—Measurement of the left ventricular activation time showed significant differentiation between cases of mitral stenosis (mean of 0.038 ± 0.008 second) and cases of mitral insufficiency (mean of 0.056 ± 0.004 second) but not between cases of mitral stenosis and cases of combined lesions, or cases of combined lesions and cases of mitral insufficiency.

TABLE II

	TYPES OF MITRAL VALVULAR DISEASE		
	PURE MITRAL STENOSIS	PURE MITRAL INSUFFICIENCY	COMBINED LESIONS
Ventricular activation time of left ventricle (sec.)	0.038 ± 0.008	0.056 ± 0.004	0.044 ± 0.003
VR_6 (in mm.)	10.21 ± 4.30	22.46 ± 7.01	13.86 ± 5.20
VS_1 (in mm.)	5.50 ± 3.69	10.43 ± 6.20	5.61 ± 3.60
$VR_6 + VS_1$ (in mm.)	15.67 ± 5.04	32.90 ± 10.38	19.47 ± 6.38

CONCLUSION

The electrocardiogram of pure mitral valvular disease, irrespective of the specific lesion, is unique in itself in that it is characterized by an SÂQRS in the frontal plane that is oriented inferiorly and, in the majority of cases, falls within Sextant V of Bayley, associated with an abnormal P wave, either fibrillating or indicative of left atrial enlargement. Certain electrocardiographic characteristics, however, permit significant differentiations between the specific lesions of pure mitral insufficiency and pure mitral stenosis and between pure mitral insufficiency and the combined lesion of mitral stenosis and insufficiency, as illustrated in Table II. No definite electrocardiographic criteria, however, could be ascertained in differentiating the combined lesion from pure mitral stenosis.

SUMMARY

Fifty-seven cases of isolated mitral valvular disease were reviewed; of these, 24 were cases of pure mitral stenosis, 15 were pure mitral insufficiency, and 18 were mitral stenosis and insufficiency. Diagnosis was based upon findings made at the time of open-heart operation, supplemented by clinical and cardiac catheterization data.

Preoperative electrocardiograms were correlated with the specific lesions in order to determine the electrocardiographic characteristics of pure mitral valvular disease and the differentiation between the specific lesions.

In general, pure mitral valvular disease, irrespective of the specific lesion, is characterized by an SÂQRS in the frontal plane that is oriented inferiorly, the majority falling within Sextant V of Bayley, associated with atrial fibrillation or signs of left atrial enlargement.

Certain electrocardiographic findings, however, characterize each specific lesion, as follows: (1) *Pure mitral stenosis:* left ventricular activation time (time of onset of intrinsicoid deflection) of 0.038 ± 0.008 second; VR_6 deflection of 10.21 ± 4.30 mm.; VS_1 deflection of 5.50 ± 3.69 mm.; $VR_6 + VS_1$ deflection of 15.67 ± 5.04 mm. (2) *Pure mitral insufficiency:* left ventricular activation time of 0.056 ± 0.004 second; VR_6 deflection of 22.46 ± 7.01 mm.; VS_1 deflection of 10.43 ± 6.20 mm.; $VR_6 + VS_1$ deflection of 32.90 ± 10.38 mm. (3) *Combined lesion of mitral stenosis and insufficiency:* left ventricular activation time of 0.044 ± 0.003 second; VR_6 deflection of 13.86 ± 5.20 mm.; VS_1 deflection of 5.61 ± 3.60 mm.; $VR_6 + VS_1$ deflection of 19.47 ± 6.38 mm.

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REFERENCES

1. Lillehei, C. W., Cohen, M., Warden, H. E., and Varco, R. L.: The Direct Vision Intracardiac Correction of Congenital Anomalies by Controlled Cross-Circulation. Results in Thirty-Two Patients With Ventricular Septal Defects, Tetralogy of Fallot, and Atrioventricular Communis Defects, Surgery **38**:11, 1955.
2. Zimmerman, H. A., editor: Intravascular Catheterization, Springfield, Ill., 1959, Charles C Thomas, Publisher.
3. Macruz, R., Perloff, J. K., and Case, R. B.: A Method for the Electrocardiographic Recognition of Atrial Enlargement, Circulation **17**:882, 1958.
4. Wilson, F. N., Kossmann, C. E., Burch, G. E., Goldberger, E., Graybiel, A., Hecht, H. H., Johnston, F. D., Lepeschkin, E., and Myers, G. B.: Recommendations for Standardization of Electrocardiographic and Vectorcardiographic Leads, Circulation **10**:564, 1954.
5. Ashman, R., and Byer, E.: The Normal Human Ventricular Gradient. I. Factors Which Affect Its Direction and Its Relation to the Mean QRS Axis (With an appendix on notation by R. H. Bayley), Am. Heart J. **25**:16, 1943.
6. Peñaloza, D., and Tranchesi, J.: The Three Main Vectors of the Ventricular Activation Process in the Normal Human Heart. I. Its Significance, Am. Heart J. **49**:51, 1955.
7. Tranchesi, J., Guimaraes, A. C., Teixeira, V., and Pileggi, F.: Vectorial Interpretation of the Ventricular Complex in Wolff-Parkinson-White Syndrome, Am. J. Cardiol. **4**:334, 1959.
8. Croxton, F. E., and Cowden, D. J.: Applied General Statistics, New York, 1955, Prentice-Hall, Inc.
9. Myers, G. B., and Klein, H.: The Electrocardiographic Diagnosis of Right Ventricular Hypertrophy, Am. Heart J. **35**:1, 1948.
10. Sokolow, M., and Lyon, T. P.: The Ventricular Complex in Left Ventricular Hypertrophy as Obtained by Unipolar Precordial and Limb Leads, Am. Heart J. **37**:161, 1949.

11. Gorlin, R., Lewis, B. M., Haynes, F. W., and Dexter, L.: Studies of the Circulatory Dynamics at Rest in Mitral Valvular Regurgitation With and Without Stenosis, AM. HEART J. **43**:357, 1952.
12. Bentivoglio, L. G., Uricchio, J. F., Waldow, A., Likoff, N., and Goldberg, H.: An Electrocardiographic Analysis of Sixty-Five Cases of Mitral Regurgitation, Circulation **18**:572, 1958.
13. Sodi-Pallares, D., and Calder, R. M.: New Bases of Electrocardiography, St. Louis, 1956, The C. V. Mosby Company.
14. Torner-Soler, M., Balaguer-Vintró, I., and Gibert-Queraltó, J.: Elevated Right Ventricular Pressure. Its Relation With the Pattern of Right Ventricular Hypertrophy, AM. HEART J. **49**:538, 1955.
15. Gibert-Queraltó, J., Torner-Soler, M., and Balaguer-Vintró, I.: The Electrocardiogram in Mitral Stenosis Before and After Commissurotomy, AM. HEART J. **49**:548, 1955.
16. Fraser, H. R. L., and Turner, R.: Electrocardiography in Mitral Valvular Disease, Brit. Heart J. **17**:459, 1955.
17. Pruitt, R. D., and Robinson, J. G.: The Electrocardiographic Findings in Patients Undergoing Surgical Exploration of the Mitral Valve, AM. HEART J. **52**:880, 1956.
18. Janton, O. H., Heidorn, G., Soloff, L. A., O'Neill, T. J. E., and Glover, R. P.: The Clinical Determination of Mitral Insufficiency When Associated With Mitral Stenosis, Circulation **10**:206, 1954.
19. Movitt, E. R., and Gerstl, B.: Pure Mitral Insufficiency of Rheumatic Origin in Adults, Ann. Int. Med. **38**:981, 1953.
20. Scott, R. C., Kaplan, S., Fowler, N. O., and Stiles, W. J.: The Electrocardiographic Pattern of Right Ventricular Hypertrophy in Mitral Valve Disease, Circulation **11**:761, 1955.
21. Grishman, A., and Dack, S.: Mitral Stenosis; Clinical, Roentgenologic, and Electrocardiographic Findings, Tr. Am. Coll. Cardiol. **6**:57, 1956.
22. Brusca, A., Stas, M. D., Levi, V., Angelico, P. F., and Dato, A.: L'electrocardiogramme precordial d'hypertrophie ventricular droite dans la maladie mitrale, Presse med. **64**:1989, 1956.
23. Bateman, R. D., and January, L. E.: The Precordial Electrocardiogram in Mitral Regurgitation, Am. J. Med. **18**:415, 1955.
24. Wierum, C., and Glenn, F.: Electrocardiographic Indications of Significant Mitral Insufficiency in Patients With Mitral Valve Disease, AM. HEART J. **53**:359, 1957.

Friedreich's Ataxia: A Neurocardiac Disease

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The cardiac manifestations of Friedreich's ataxia were reported in the early descriptions of the disease. Five of the original six patients whose cases were reported by Friedreich[1] (1863) had cardiac abnormalities. Pitt[2] (1887) reported a case in which there was congestive failure and diffuse myocardial fibrosis at autopsy.

Generally, however, the disease has been considered a familial neurological disturbance which affects the posterior and lateral columns of the spinal cord and results in skeletal deformities, ataxia, and speech disturbance. Histologically, the tracts of Goll and Burdach, the pyramidal tracts, Clarke's column, and the dorsal spinocerebellar tracts show advanced degeneration with gliosis. White matter is affected, whereas ganglion cells are only secondarily involved.

An increasing appreciation of the frequency of cardiac involvement is apparent in the recent literature; Manning[3] reports an incidence of 30 per cent.

We feel that the cardiac lesion is an intrinsic component of the disease and have found support for this in the reports of Russell,[4] Nadas,[5] and Schilero.[6] The electrocardiogram was shown by Evans and Wright[7] to be an important diagnostic adjunct.

Seven documented cases of Friedreich's ataxia which were seen at the Ohio State University Health Center since 1954, form the basis for this report. One patient is reported in detail in order to demonstrate the clinical manifestations of the "myocarditis" associated with this disease.

CASE REPORT

F. C., a 33-year-old white woman, was first seen at the Ohio State University Outpatient Department in October, 1954, because of a furuncle of the scapular region. She was described as being a poorly nourished spastic quadriplegic. Physical findings of generalized weakness, diminution of deep tendon reflexes, and bilateral Babinski sign were recorded. A diagnosis of cerebral palsy was made. In a subsequent visit, after local treatment for the furuncle, it was learned from the family that a diagnosis of Friedreich's ataxia had been made when she was 22 years old. Her first symptom had been weakness, manifested at the age of 18 years. Severe speech disturbance and difficulty in walking began at age 21.

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Family history revealed that a younger brother had been similarly affected, but there were also eight normal siblings, and the parents were living and well. An electrocardiogram was ordered because of irregularity of rhythm, and this showed sinus rhythm with frequent ventricular premature contractions. There was, in addition, low voltage of the QRS, and minimal nonspecific T-wave changes. A chest x-ray film was interpreted as showing 15 per cent increase in the transverse cardiac diameter.

The patient was not seen again until June, 1957, when she was brought to the emergency room with complaints of severe cough, dyspnea, restlessness, and palpitation of about 8-day duration. Virtually no history could be obtained directly from the patient, but she appeared to understand questions and could communicate with signs and monosyllables.

Physical examination disclosed an orthopneic, pale, dishevelled, and diaphoretic patient with a nasal type of slurred speech. The heart rhythm was grossly irregular, with an apical rate of 180 per minute. There was tachypnea of 35 per minute. The blood pressure was 130/110 mm. Hg. Râles were heard in the chest, and the heart was enlarged to the left anterior axillary line. No cardiac murmurs were heard. There was some variation in the intensity of the first heart sound, and the second pulmonic sound was increased. The liver was palpable 2 fingerbreadths below the right costal margin in the mid-clavicular line, and there was 4+ pitting ankle edema. The eyes showed rotary nystagmus and optic atrophy. Skeletal deformities included a high arched palate, bilateral pes cavus, and talipes equinovarus. Neurological examination revealed absent deep tendon reflexes, bilateral Babinski signs, and gross ataxia of all extremities. Superficial abdominal reflexes were present. An electrocardiogram taken at the time of admission showed only atrial fibrillation.

One hour after an intravenous dose of 0.4 mg. of lanatoside-C the electrocardiogram showed atrial flutter with 2:1 atrioventricular block and a ventricular rate of 180 per minute. This was not affected by carotid sinus pressure. The rhythm fluctuated between atrial flutter and atrial fibrillation in the next 4-hour period, but the ventricular rate slowed to 150 to 160 per minute, and the patient's dyspnea improved. She was given 2 c.c. of Mercuhydrin intravenously and two additional injections of 0.4 mg. lanatoside-C at 4-hour intervals. Twelve hours after admission the ventricular rate had slowed to 110 per minute, and the rhythm was atrial fibrillation. The patient was in no distress at the time, and a standard chest film showed an increase in the transverse cardiac diameter and pulmonary hyperemia.

Laboratory examinations, which included a hemogram, urinalysis, serologic tests for syphilis, antistreptolysin titer, and C-reactive protein, were normal. An attempt to convert the rhythm from atrial fibrillation to normal sinus rhythm with quinidine was abandoned because of frequent ventricular premature contractions. The only specific medication given during the remainder of her hospitalization was 0.25 mg. of digoxin daily. A loss of weight of 10 pounds during the first 7 hospital days was attributed to diuresis, and the patient was discharged on the twelfth hospital day with instructions to continue the digoxin and to limit her intake of salt.

In February, 1958, the patient was admitted from the outpatient department with a supraventricular tachycardia and a ventricular rate of 180 per minute. Again the rhythm fluctuated between atrial flutter and fibrillation. Atrial fibrillation with a slow ventricular rate persisted after rapid redigitalization with digoxin. During this admission the rhythm was converted to sinus with quinidine, and when she was discharged, the patient was advised to continue taking quinidine, 0.3 Gm. every 6 hours, and digoxin, 0.25 mg. daily.

In September, 1959, the patient again had atrial fibrillation but was free from cardiac symptoms. She had deteriorated generally, and is now confined to a wheel chair in a nursing home, with the gloomy prognosis that attends this disease.

RÉSUMÉ OF SEVEN CASES

Four women and three men are included in this group; none is related to another. The average age at the onset of symptoms was 13 years. Two patients gave a positive family history for the disease, and a questionable history was obtained in a third case.

Six patients had noticeable speech impediments, and nystagmus was present in six. Ataxia and diminution or absence of deep tendon reflexes were constant findings. Superficial reflexes were present in all patients except one 46-year-old woman.

TABLE I

PATIENT, SEX, AGE	AGE AT ONSET (YR.)	FAMILY HISTORY	SPEECH DISTURBANCE*	NYSTAGMUS*	ATAXIA*	SUPERFICIAL REFLEXES	DEEP REFLEXES	PATHOLOGIC REFLEXES	POSTERIOR COLUMN FUNCTION	DEFORMITIES		ELECTROCARDIOGRAM
										F. F.†	K. S.‡	
1. D. A. M, 43	17	None	+++	+	+++	+	Absent	+	Diminished	+	+	Myocardial changes suggesting ischemia (symmetrical T-wave inversion in V_3 and V_4)
2. J. B. F, 17	7	2 cousins with cerebral palsy	+	−	+++	+	Absent	+	Normal	+	+	Low voltage of T waves
3. K. E. M, 28	7	None	+	+	++	+	Absent	+	Diminished	+	+	Axis 180°. Atrial fibrillation. Low voltage. Incomplete right bundle branch block
4. J. F. M, 23	6	Cousin in Italy similarly afflicted	++	+	++	+	Absent	+	Slightly diminished	+	+	Myocardial changes. Flat T waves with inversion in V_6. Low voltage
5. J. S. F, 46	24	None	+	+	++	Absent	Absent	Absent	Diminished	+	−	Subendocardial ischemia
6. A. C. F, 25	13	None	−	+	+	+	Diminished in arms; absent in legs	+	Diminished	+	−	Not recorded
7. F. C. F, 33	18	Brother died with congestive heart failure at age 24	++++	++	+++	+	Absent	+	Poor	+	+	Atrial fibrillation and flutter. Low voltage and nonspecific T-wave changes. Incomplete right bundle branch block

*Graded 1+ to 4+.
†F.F.: Friedreich's foot.
‡K.S.: Kyphoscoliosis.

Friedreich's foot was present in every patient and represents the *sine qua non* of this disease. Pathologic toe signs were present in six patients, and kyphoscoliosis in five. Signs in the posterior column were variable; there were abnormal findings in all but one patient.

The electrocardiogram was abnormal in the six patients on whom it was recorded. Two patients had atrial fibrillation, and two others showed symmetrical T-wave inversion. Low voltage and nonspecific T-wave changes were the most common findings. Incomplete right bundle branch block was present in two patients and raises the possibility of kyphoscoliotic heart disease, which may produce this electrocardiographic pattern.

Only the previously described patient (F. C.) had significant cardiac complaints. Organic murmurs were not heard in any of the patients. Significant data concerning these patients are outlined in Table I.

DISCUSSION

Myocardial changes have usually been ascribed to lesions of the medulla which involve the vagal nuclei facilitating sympathetic overactivity.[8] The changes in the myocardium reported by Russell are focal necrosis with collagenous replacement and compensatory hypertrophy of surviving muscle. The chronic degenerative process may result in heart failure, and severe fatty degeneration is a terminal phase. None of Russell's four cases showed involvement of the vagal nuclei, and all revealed chronic interstitial myocarditis. These findings support a toxic origin of the disease and justify her conclusion that the inheritance of a lethal gene affects both the heart and central nervous system.

Loiseau's review included 16 autopsy cases, all but one of which showed cardiac abnormalities. The actual incidence of myocarditis cannot be definitely determined from reported autopsy findings, since microscopic lesions could be missed in grossly normal hearts.

Evans and Wright found abnormal electrocardiograms in 12 of 38 cases, but an additional 10 patients had borderline electrocardiographic abnormalities. Only one of their patients had clinical heart disease. The electrocardiogram has been reported to show all the common atrial arrhythmias, atrioventricular block, bundle branch block, chamber enlargement, and, most frequently, nonspecific T-wave changes. The limb leads may show changes simulating myocardial infarction.

Manning reported four cases of Friedreich's ataxia with cardiac manifestations, and in one of those cases there was autopsy confirmation of myocarditis. Two additional patients did not have cardiac lesions but the diagnosis was somewhat in doubt. Hejtmancik and associates[9] reported necropsy findings of chronic interstitial myocarditis in one case.

Nadas and associates reported five children who had abnormal electrocardiograms, and ventricular parasystole and pericardial effusion were present in two of these children, findings which had not been previously reported in cases of the disease. One autopsy case showed diffuse myocardial fibrosis.

Schilero and associates presented a comprehensive review of the literature and reported 11 additional cases of Friedreich's ataxia. A single autopsy case showed chronic interstitial myocarditis.

Pathologic findings in the heart have been reported in all of the autopsy cases of Friedreich's ataxia which we have reviewed. These findings are usually described as chronic interstitial myocarditis.

Clinical evidence of heart disease was found in only one of our cases, but the electrocardiographic changes in five additional cases suggest the presence of heart disease.

On the basis of both our own experience and the findings in the literature, we have concluded that involvement of the heart is a common, if not constant, feature of cases of Friedreich's ataxia.

SUMMARY

Seven cases of Friedreich's ataxia are reported, and in six of these, electrocardiograms were recorded, all of which were abnormal. A review of the literature discloses increasing awareness of the cardiac aspects of the disease.

We find that in every autopsied case reported upon in the American and English literature there were abnormal findings in the heart; usually, these were findings of chronic interstitial myocarditis.

We believe that Friedreich's ataxia is a neurocardiac disease which involves both the central nervous system and the heart.

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REFERENCES

1. Friedreich, N.: Über degenerative Atrophie der spinalen Hinterstränge, Arch. f. Anat. u. Physiol. **26**:391 and 433, 1863; **27**:1, 1863; **68**:145, 1876; **70**:140, 1877.
2. Pitt, G. N.: On a Case of Friedreich's Disease: Its Clinical History and Postmortem Appearance, Guy's Hosp. Rep. **44**:369, 1887.
3. Manning, G. W.: Cardiac Manifestations in Friedreich's Ataxia, AM. HEART J. **39**:799, 1950.
4. Russell, D. S.: Myocarditis in Friedreich's Ataxia, J. Path. & Bact. **58**:739, 1946.
5. Nadas, A. S., Alimurung, M. M., and Sieracki, L. A.: Cardiac Manifestations of Friedreich's Ataxia, New England J. Med. **244**:239, 1951.
6. Schilero, A. J., Antzis, E., and Dunn, J.: Friedreich's Ataxia and Its Cardiac Manifestations, AM. HEART J. **44**:805, 1952.
7. Evans, W., and Wright, G.: Electrocardiogram in Friedreich's Ataxia, Brit. Heart J. **4**:91, 1942.
8. Loiseau, J.: Les troubles cardiaques dans la maladie de Friedreich, Thèse de Paris, 1938.
9. Hejtmancik, M. R., Bradfield, J. Y., Jr., and Miller, G. V.: Myocarditis and Friedreich's Ataxia, AM. HEART J. **38**:757, 1949.
10. Hassin, G. B.: Friedreich's Ataxia: a Histopathologic Study, Arch. Neurol. & Psych. **39**:116, 1938.

Pericarditis Following Mild or Silent Coronary Episodes: An Attempt at Narrowing the Field of Idiopathic Pericarditis

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Acute myocardial infarction is sometimes complicated by pericarditis, pleurisy, and pneumonitis. The complication has been termed "postmyocardial infarction syndrome."[1,2] Although it is mostly associated with extensive myocardial infarction, the condition has been observed to follow also minor coronary eipsodes.[2] The clinical and laboratory features as well as the course of the postmyocardial infarction syndrome resemble in every way idiopathic benign pericarditis. The complication of myocardial infarction is distinguished by its close relation to a preceding coronary attack. If, however, the coronary episode is silent or causes only minor symptoms and signs, and there is a lapse of several weeks between the coronary attack and the appearance of pericarditis, the causal relationship is obscured. The condition presents then a puzzling diagnostic problem, and "idiopathic" pericarditis is often diagnosed. It is the purpose of this report to draw attention to such cases which are erroneously assigned to the group of idiopathic pericarditis.

CASE REPORTS

CASE 1.—M. S., a 71-year-old man, was admitted to the Maimonides Hospital for the fourth time on July 28, 1958, because of fever and pain in the temporomandibular joints which had lasted for 2 weeks. The patient was said to have sustained a myocardial infarction in 1949. Since 1956, he had suffered from angina of effort and episodes of heart failure. From November, 1957, to May, 1958, he was hospitalized three times because of hypertensive-arteriosclerotic heart disease, A-V block, and Adams-Stokes attacks.

On the last hospital admission the temperature was 101°F., pulse was 60, respirations were 24, and the blood pressure was 140/80 mm. Hg. The neck veins were distended. Râles were heard over both pulmonary bases. The heart seemed to be enlarged bilaterally. Considerable retrosternal dullness suggested the presence of pericardial effusion. A harsh systolic murmur was heard along the left margin of the sternum, at times followed by a short diastolic murmur. The liver was palpable six fingerbreadths below the right costal margin. The tip of the spleen could be felt below the left costal arch.

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Laboratory Data.—The urine contained 1 to 2-plus albumin and, at one examination, 30 to 40 red blood cells per high-power field. Hemoglobin was 8.8 Gm. per cent. The white blood cell count ranged from 9,000 to 18,000, with an increase in the polymorphonuclear cell count; sedimentation rate (Wintrobe) was 30 mm./hr.; blood urea nitrogen was 38 mg. per cent; serum glutamic oxalacetic transaminase was 12 units. Blood cultures yielded no growth. The electrocardiogram showed atrial fibrillation and left bundle branch block. There were no signs of myocardial infarction.

Course.—During the first 5 hospital days the temperature ranged from 101 to 102°F., and then returned to normal. Since subacute bacterial endocarditis was suspected, large doses of penicillin and streptomycin were given. On the fourth hospital day a loud pleuropericardial friction rub was heard. Roentgenographic study (Fig. 1) of the chest showed increase of the transverse diameter of the heart. The left leaf of the diaphragm was obscured, which was attributed to pleural effusion.

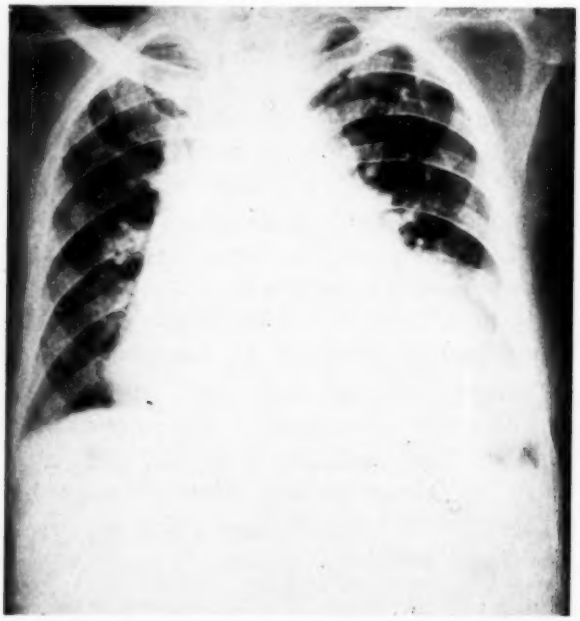

Fig. 1.—Case 1. The cardiac silhouette is enlarged and the left leaf of the diaphragm is obscured.

In spite of the return of the temperature to normal, the clinical course was downhill. The blood urea nitrogen rose to 58 mg. per cent. The friction rub persisted and dyspnea increased; but the blood pressure was well maintained. The patient expired on the ninth hospital day, in the fourth week of his illness. The clinical diagnosis was: arteriosclerotic and rheumatic heart disease; rheumatic carditis including pericarditis or possibly subacute bacterial endocarditis.

Postmortem examination revealed about 600 ml. of fluid in each pleural cavity. The lungs showed congestion but no consolidation. No clots were found in the pulmonary arteries. The pericardial sack contained 700 ml. of hemorrhagic fluid. The epicardium and pericardium were covered with thick, granular, fibrinous material. The heart weighed 550 grams. The wall of the right ventricle measured 0.5 cm., and that of the left ventricle measured 2.3 cm. The posterior portion of the interventricular septum near the apex showed a hemorrhagic area with yellowish-gray and dark brown spots. The average diameter of the infarcted area was 2 cm. Focal gray zones were noted in the posterior papillary muscle and in subendocardial areas of the left ventricle near the septum. The leaflets of the aortic valves were thickened and slightly rigid. There was fusion of the commissure of the right and posterior cusps, and calcification at the base of the valve.

The pathologist estimated that the myocardial infarction was from 3 to 5 weeks old, and that the pericarditis was from 2 to 4 weeks old. He thought that the pericarditis was secondary to the recent small myocardial infarction which had caused neither symptoms nor diagnostic signs.

CASE 2.—R. G., a 57-year-old woman, was admitted to the Maimonides Hospital for the first time on Jan. 11, 1954, because of shortness of breath and swelling of the ankles. She suffered from diabetes and hypertension. At no time did she complain of anginal distress. Six weeks prior to admission, shortness of breath developed rather abruptly. Three weeks later, pleural effusion was noted.

On admission the temperature was 103°F. There were signs of failure of the left and right sides of the heart. A marked pleural effusion on the left side required repeated paracenteses, which yielded up to 1,000 ml. of greenish-yellow fluid that clotted readily.

On the fourth hospital day the patient complained of pain in the chest which was aggravated by breathing. A pericardial friction rub appeared and remained audible for several weeks. There was leukocytosis of 11,700, with 83 per cent neutrophil cells. The sedimentation rate was 47 mm./hr. (Wintrobe). Roentgenographic study revealed enlargement of the cardiac silhouette, which, after 10 days, was distinctly diminished. Another increase in the size of the cardiac shadow was observed at a later flare-up in the seventh hospital week; again, this was followed by a reduction in size.

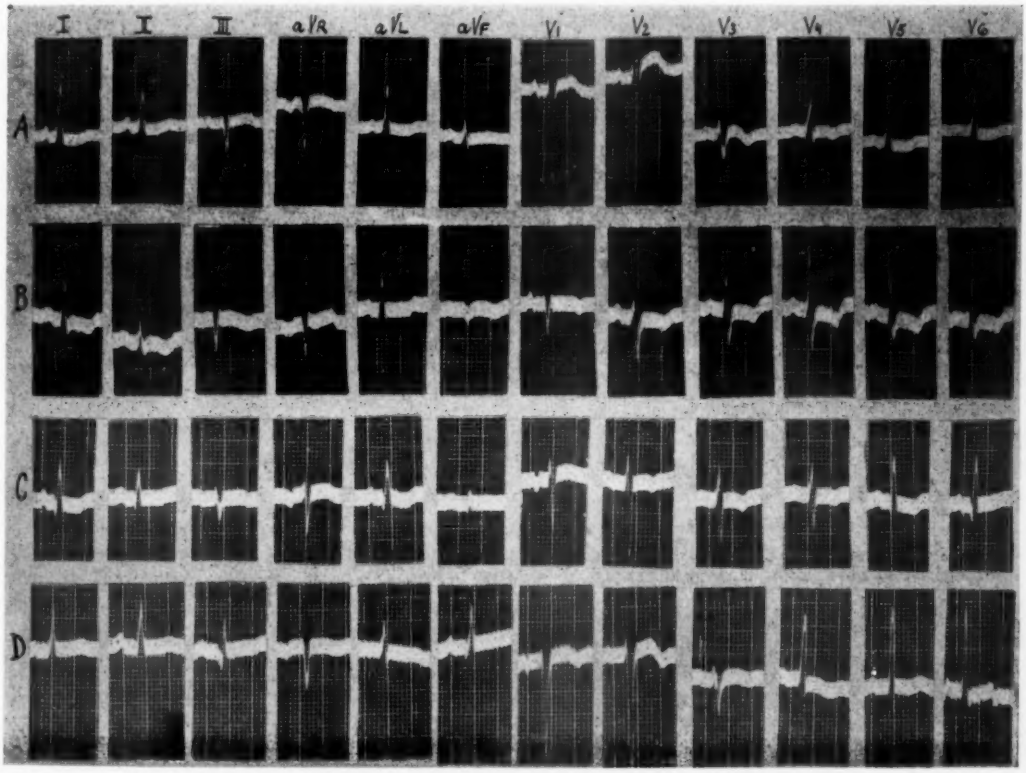

Fig. 2.—*A*, Signs suggestive of left ventricular hypertrophy and digitalis effect. Inversion of T in Leads V_3 and V_4 might be compatible with an ischemic lesion of the anterior wall or with pericarditis. *B*, Lead aV_F shows a small QS deflection and inversion of T. In Lead III the T wave is inverted. These changes may be due to an ischemic lesion of the posterior wall. The S-T segment is depressed and the T wave inverted in most of the precordial leads, in Leads I, II, and aV_L. (The patient has been digitalized.) *C*, There are nonspecific changes of the S-T segment and T wave. Inversion of T in the precordial leads would be compatible with pericarditis. *D*, Signs suggestive of left ventricular hypertrophy. A wide and slurred Q wave in Leads III and aV_F suggests old posterior wall infarction. Inversion of T in the right-sided precordial leads might be compatible with either pericarditis or an ischemic lesion of the anteroseptal wall.

The cause of the pleuropericarditis was obscure. Myocardial infarction was considered but the clinical data did not support this diagnosis. The electrocardiographic findings were inconclusive. Changes in the electrocardiogram were thought to be compatible with left ventricular hypertrophy and digitalis effect (Fig. 2,*A*). Inversion of the T wave in Leads V_3 and V_4 might have been due to an ischemic lesion or pericarditis. Cultures of the aspirated pleural fluid yielded no growth. A tuberculin skin test in a concentration of 1:1000 was negative. No acid-fast bacilli could be found in several gastric washings. Search for lupus erythematosus cells in the blood was unsuccessful.

Irregular fever, with elevation of temperature up to 104°F., persisted for 5 weeks. Large doses of penicillin and streptomycin did not seem to affect the course. An abrupt fall in temperature occurred after the administration of aspirin, and the temperature remained then at a normal level. The general condition improved, but congestive heart failure persisted. The patient expired a year later, after sudden aggravation of dyspnea. There was again nothing in the patient's complaints nor in the electrocardiogram to indicate a myocardial infarction.

Postmortem examination revealed marked narrowing of the coronary arteries by arteriosclerosis. The left circumflex branch was occluded by a recent thrombus. A recent myocardial infarction occupied large portions of the posterolateral wall of the left ventricle. Healed infarctions were found in the posterior and anteroseptal areas. There was chronic adhesive pericarditis for which no cause could be found other than the old myocardial infarction.

CASE 3.—T. S., a 56-year-old diabetic woman, was admitted to the Maimonides Hospital on May 31, 1956, because of fever and chest pain. At the end of April, 1956, she developed a tightening sensation in the substernal region, neck, and jaws, associated with a rise in temperature. The painful sensation was aggravated by drawing a deep breath and turning in bed. Pain and fever subsided after a few days, but recurred soon, and the patient was hospitalized elsewhere on May 12, 1956. On May 16, the pain shifted to the left shoulder and arm. The temperature remained elevated for 17 days and reached peaks of 104°F.

Serial x-ray studies revealed progressive enlargement of the heart silhouette. Patches of infiltration were noted in both lungs, and there was bilateral pleural effusion. The electrocardiogram showed changes which caused the presence of an ischemic lesion in the posterior wall to be suspected. However, the nature of the prolonged febrile condition and its relationship to the changes in the electrocardiogram were not clear. Antibiotics had no effect. On the eighteenth hospital day a pericardial friction rub was heard for the first time.

On May 31, 1956, the patient was transferred to the Maimonides Hospital for further study. There, the findings of pericarditis, pleurisy, and pneumonitis were confirmed. An electrocardiogram taken on June 1, 1956 (Fig. 2,*B*), showed a small QS deflection and inverted T wave in Lead aV_F, and inversion of T in Lead III. There were depression of the S-T segment and inversion of T in most of the precordial leads as well as in Leads aV_L, I, and II. These features were compatible with pericarditis and digitalis effect. The changes in Leads III and aV_F were suspicious but did not represent dependable evidence of posterior wall myocardial infarction, in the absence of a history of a full-blown coronary attack. However, a thorough investigation of the events which preceded the febrile illness elicited the following data. About 8 weeks prior to the onset of the febrile illness the patient had been shoveling snow. For the first time then she experienced pain across her chest which forced her to give up the unaccustomed work, whereupon the chest distress promptly subsided. In the following weeks the patient was free of complaints, and the transient chest pain was all but forgotten, when, after a lapse of 2 months, the present illness developed. On the basis of the history it was concluded that the triad of pericarditis, pleurisy, and pneumonitis presented sequelae to an acute coronary episode which had occurred 8 weeks before and had manifested itself only by transient occurrence of angina of effort.

CASE 4.—R. G., a 69-year-old woman who was suffering from diabetes, was admitted to the Maimonides Hospital on Aug. 24, 1958, because of severe chest pain and fever. Three years prior to admission she experienced substernal pain which radiated to the back and left arm, in association with effort and excitement. The distressing sensation was promptly relieved by nitroglycerin. On occasions the pain was even felt when the patient rested. She was hospitalized elsewhere on June 9, 1958, because of increased incidence and severity of the anginal attacks. After

her condition had improved, she was discharged on June 29, 1958. About 2 months after this hospitalization the patient began to complain of a "pleural type" of chest pain which was aggravated by deep inspiration and coughing. There was no bloody expectoration nor evidence of phlebitis in the legs. The temperature rose at times to 103.5°F. Antibiotics were ineffective. X-ray study of the chest indicated left pleural effusion and enlargement of the heart shadow.

After admission to the Maimonides Hospital, the fever and chest pain persisted. There was leukocytosis, with increase of the neutrophil count, and the sedimentation rate was elevated. A chest consultant diagnosed pleuritis and performed a pleural tap. A straw-colored fluid was obtained which contained neither tumor cells nor acid-fast bacilli. Several blood cultures were negative. Search for lupus erythematosus cells in the blood was unsuccessful. A pericardial friction rub was first heard on Aug. 27, 1958, and remained audible for 3 days. Percussion showed an increase in the area of absolute cardiac dullness. X-ray study, on August 25 (Fig. 3,*A*), revealed, in addition to left-sided pleural effusion, widening of the waist and marked increase in the transverse diameter of the heart silhouette, as well as disappearance of the subdivisions of the left contour, compatible with pericardial effusion.

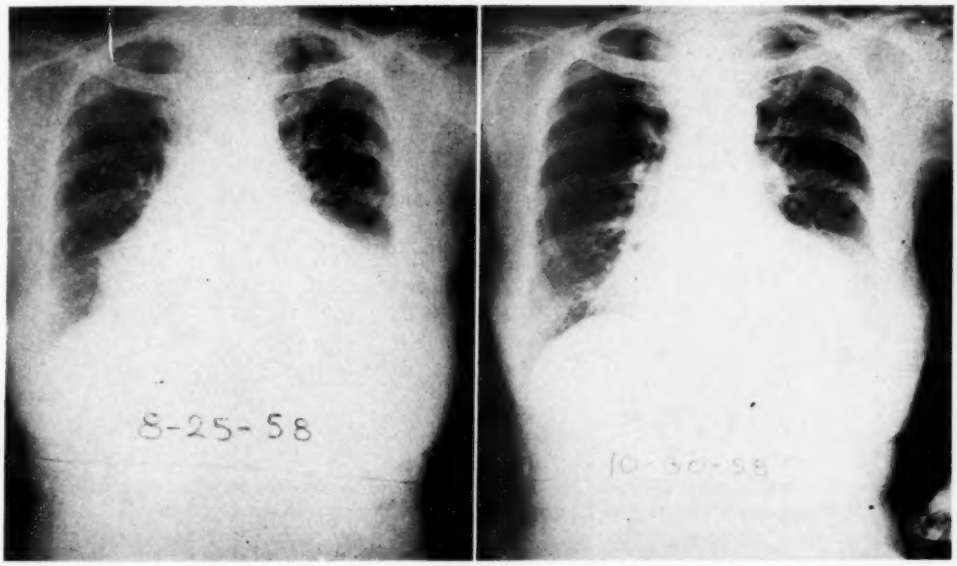

Fig. 3.—Case 4. *A*, The transverse diameter of the heart is increased and the waist is widened. The normal subdivisions of the left contour are not visible. There is left pleural effusion. *B*, Two months after *A*. The size of the heart silhouette is decreased, and the subdivisions of the left contour are again visible.

The nature of the condition was obscure. An electrocardiogram taken on Aug. 8, 1958 (Fig. 2,*C*), and several tracings therafter, failed to show evidence of myocardial infarction. There were only nonspecific changes of the S-T segment and of the T wave. Inversion of the T wave in precordial leads could be due to pericarditis. Determination of the serum glutamic oxalacetic transaminase showed values of 56 units on August 27, and 49 units on September 2. An inquiry at the hospital at which the patient had been treated 8 weeks previously revealed that electrocardiograms taken at that time had shown sharply inverted T waves in Leads V_2 through V_6. An ischemic lesion of the anterior wall had been diagnosed. Significant changes of QRS were absent. We therefore concluded that the present febrile condition represented a late sequela to ischemic myocardial necrosis. The exceedingly painful condition subsided coincident with salicylate therapy after a duration of 5 weeks. A follow-up x-ray study on Oct. 30, 1958 (Fig. 3,*B*), revealed reduction in the size of the cardiac silhouette, and especially of its waist, and reappearance of the normal subdivisions of the left cardiovascular contour.

CASE 5.—B. W., a 57-year-old woman who suffered from hypertension, was admitted to the Maimonides Hospital on May 20, 1957, because of fever and chest pain. For the previous 2 years the patient had complained of precordial pain which was associated with effort and promptly relieved by rest. In February, 1957, she suffered bilateral pneumonia. In the first half of May, 1957, fever developed, and the patient complained of severe pain in the chest and shoulders, which was aggravated by breathing and lying down, and was relieved by sitting up. A chest consultant diagnosed left-sided pleuritis. On admission the temperature was 101.2°F. Over the lower lobe of the left lung, flatness to percussion and diminished breath sounds were noted. Palpation of a heaving apical impulse of the heart indicated left ventricular hypertrophy. Marked dullness was percussed over the lower end of the sternum and in an area adjacent to the sternum in the fifth left intercostal space. A pericardial friction rub was not audible.

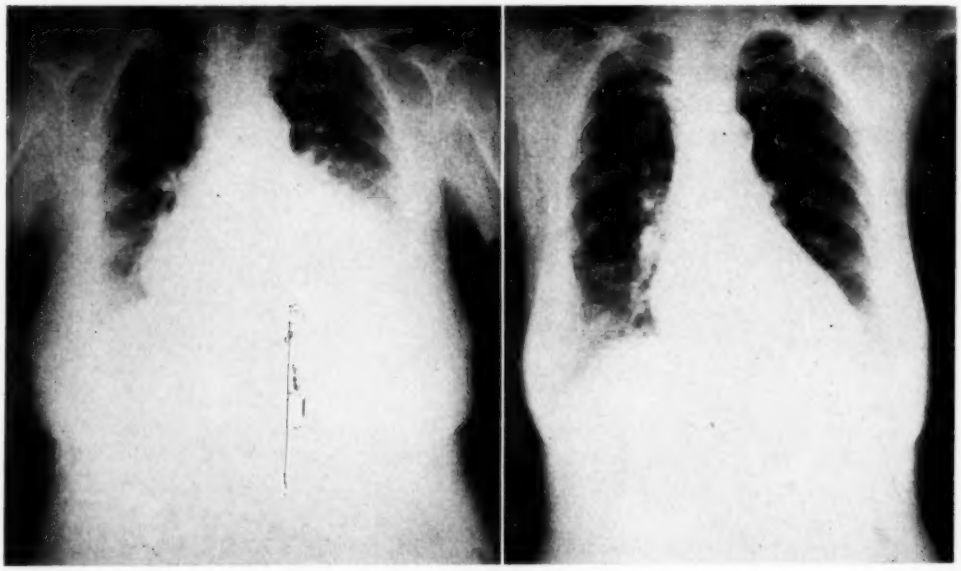

Fig. 4.—Case 5. *A*, The cardiac silhouette is enlarged and there is evidence of bilateral pleural effusion. *B*, Six weeks after *A*. The size of the cardiac silhouette is markedly reduced.

Significant laboratory findings were: hemoglobin of 10.3 Gm. per cent; white blood cell count of 17,800, with 73 per cent neutrophils; sedimentation rate of 37 mm. per hour (Wintrobe); and fasting blood sugar of 125 mg. per cent. X-ray study of the chest (Fig. 4,*A*) revealed bilateral pleural effusion, predominantly at the left side, and a marked increase in the transverse diameter of the heart shadow, which appeared to indicate enlargement of the heart. An electrocardiogram on May 20 (Fig. 2,*D*), showed signs of left ventricular hypertrophy. A wide and slurred Q wave in Leads III and aV_F suggested old posterior wall infarction. Inversion of the T wave in the precordial leads of the right side was compatible with either pericarditis or an ischemic lesion of the anterior wall.

Course.—The patient's condition improved temporarily following admission. On the tenth hospital day the temperature rose to 103°F. Severe chest pain made it difficult for the patient to draw a deep breath. The white blood cell count climbed to 25,000. On June 6, pleural paracentesis produced 800 ml. of serosanguineous fluid, in which neither tumor cells nor acid-fast bacilli were found. Culture of the aspiration fluid yielded no growth. A search for acid-fast bacilli in the sputum was unsuccessful.

Pleural paracentesis was followed by short-lasting improvement. During the second half of June, the chest pain again became severe. The electrocardiogram showed no significant new changes. Administration of antibiotics failed to influence the course. A cardiologic consultant was impressed with the "coronary" history and especially with the fact that anginal attacks of

marked severity, requiring injection of analgesics for relief, had occurred about 3 months prior to the present illness. Because no other cause was found, it was felt that pleuropericarditis might be secondary to arteriosclerotic heart disease. When the effusions proved obstinate and the chest pain kept on recurring, the administration of prednisone was started on June 23. This was followed by dramatic improvement. On July 3, x-ray study (Fig. 4,*B*) revealed a marked reduction in the size of the heart silhouette. The patient was discharged on July 10, 1957. During the following 5 weeks the dosage of prednisone was gradually reduced and then discontinued. Withdrawal of the steroid was not followed by a relapse.

COMMENT

During the study of the postmyocardial infarction syndrome it became apparent that "coronary" pericarditis was not necessarily associated with extensive myocardial infarction but sometimes followed minor coronary episodes.[2] Such cases present a puzzling diagnostic problem, especially when myocardial necrosis remains silent or when a period of many weeks elapses between the coronary episode and recognition of the pericarditis. The condition may appear to belong to the group of idiopathic pericarditis. In fact, Case 2 was originally published under this label[3] before postmortem examination revealed the presence of recent and old myocardial infarctions in the absence of other known causes of pericarditis. In Case 1, necropsy showed a large hemorrhagic pericardial effusion for which the pathologist could find no cause other than a small myocardial infarction which appeared to be slightly older than the pericarditis. In both instances (Cases 1 and 2), myocardial infarction had manifested itself neither by clinical symptoms and signs nor by significant electrocardiographic changes. A protracted febrile condition with evidence of pleuropericarditis was the predominant feature of the illness.

In Cases 3 and 4 the relationship of the pericarditis to the preceding coronary attack was obscured by two circumstances. First, the coronary episodes had caused only minor symptoms and signs. The electrocardiogram, in particular, failed to show well-defined changes characteristic of a recent myocardial infarction. Second, the pericarditis was not discovered until 8 weeks after the acute coronary episode. In Case 5 the pericarditis could not be traced to an acute coronary attack, although the electrocardiogram showed suspicious evidence of old myocardial infarction. There was a history of angina pectoris of many years' duration. Furthermore, the anginal attacks had increased in severity and frequency about 3 months prior to the onset of the pleuropericarditis. Diligent search failed to reveal any of the well-known etiological factors of pericarditis. After the extremely painful condition had resisted all therapeutic attempts for 6 weeks, it was dramatically and permanently relieved by the administration of corticosteroids.

It is of interest that 4 of the 5 patients were women. Coronary arteriosclerosis occurs less frequently in females; hence, coronary origin of pericarditis may not even be suspected in a female.

The term "idiopathic" is undesirable because it serves only to cover up ignorance of etiology. In a previous report,[3] attention was drawn to the fact that instances of pericarditis published as idiopathic pericarditis were observed in patients who had rheumatic valvular lesions. In a number of instances the

Coxsackie virus was reported as the cause of benign pericarditis.[4] The observations described in the present report should open the way for separation of another small group from the trash basket of idiopathic pericarditis. When patients with unexplained pericarditis, especially those of the older age groups, present a family history of diabetes, stroke, hypertension, or arteriosclerotic heart disease, coronary origin of the pericarditis may be suspected even in the absence of evidence of recent myocardial infarction. A thorough search into the patient's personal history may reveal, as it did in the cases of this report, the occurrence of angina pectoris, and perhaps previous acute coronary episodes, in support of a diagnosis of "coronary" pericarditis.

The term "coronary" pericarditis is used to denote a condition which is often associated with pleurisy and pneumonitis, and occurs secondary to arteriosclerotic heart disease. Large or small areas of ischemic myocardial necrosis are probably the determining factor. When coronary pericarditis is preceded by a well-defined myocardial infarction, it is referred to as "postmyocardial infarction syndrome." When no clear relationship with a myocardial infarction can be established, the diagnosis of "coronary" pericarditis can be made with great probability in the presence of symptoms and signs of coronary arteriosclerosis, when other known etiological factors of pericarditis have been excluded. The diagnosis is sometimes a guide to effective therapy, as the observations in Case 5 have shown.

SUMMARY

"Coronary" pericarditis represents a syndrome consisting of pericarditis, pleurisy, and pneumonitis, which develops secondary to arteriosclerotic heart disease. It can be readily diagnosed when it follows shortly after a well-defined myocardial infarction. However, when the acute coronary episode is mild or silent, and there is a lapse of many weeks between the coronary attack and the appearance of pericarditis, the causal relationship may be obscured and idiopathic pericarditis diagnosed. Five cases are reported to illustrate this point.

The search for etiology in any given case of pericarditis should include among other causes "coronary" origin. Diagnostic considerations of this kind will result in the separation of cases hitherto assigned to idiopathic pericarditis and in the reduction of this undesirable group.

REFERENCES

1. Dressler, W.: A Postmyocardial Infarction Syndrome. Preliminary Report of a Complication Resembling Idiopathic, Recurrent, Benign Pericarditis, J.A.M.A. **160**:1379, 1956.
2. Dressler, W.: The Postmyocardial Infarction Syndrome. A Report on 44 Cases, A.M.A. Arch. Int. Med. **103**:28, 1959.
3. Dressler, W.: Idiopathic Recurrent Pericarditis, Am. J. Med. **18**:591, 1955.
4. Gillett, R. L.: Acute Benign Pericarditis and the Coxsackie Virus, New England J. Med. **261**:838, 1959.

Electrocardiographic Abnormalities in Acute, Convalescent, and Recurrent Stages of Idiopathic Pericarditis

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Analysis was made of the electrocardiographic characteristics of acute, convalescent, and prolonged follow-up phases of benign idiopathic pericarditis. Thirty-one cases were observed for periods of from 6 months to 10 years. Three patients manifested persistent S-T segment or T-wave abnormalities for 17 months, 19 months, and 10 years, respectively. A review of 475 cases described by 39 authors[1-39] reveals that 234 cases had follow-up observations, and that 13 cases[1-6] demonstrated electrocardiographic changes that lasted longer than 3 months. These data suggest that this so-called acute and benign syndrome may be followed by long-lasting myocardial pathology. Certain clinical and pathologic observations validate this assumption, for there are reports of permanent arrhythmias,[22] pericardial calcification[1] or fibrosis,[7] and constrictive pericarditis[6] directly related to acute and recurrent attacks of idiopathic pericarditis. Indeed, surgical intervention (pericardiectomy) has been used in 8 cases[40] to relieve chronic and profound hemodynamic abnormalities produced by such changes. These observations indicate that earlier assurances[24] that idiopathic pericarditis leaves no residual myocardial damage are unfortunately unfounded.

THE ELECTROCARDIOGRAM IN THE ACUTE PHASE OF IDIOPATHIC PERICARDITIS

It is today a universal assumption that the S-T segment and T-wave changes in acute pericarditis are manifestations of subepicardial injury. Elucidation of this phenomenon was accomplished by investigators working in the laboratory in 1932,[41] and 1939,[42] and substantiated by clinical and postmortem study in 1937,[43] and 1938.[44] A characteristic electrocardiographic pattern of the acute phase was described which included concavity upward of the S-T segments and peaking of the T waves.[23]

The electrocardiograms of the acute phase of idiopathic pericarditis were studied in a group of 31 patients which consisted of 21 men and 10 women with

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an average age of 41.9 years, and were compared to 325 cases from the literature[25] (Table I). Four cases, or 13 per cent, of my patients, experienced transient episodes of auricular fibrillation during their illness. This is the exact incidence recorded by Scherl[22] in his report of 30 cases of idiopathic pericarditis. It was interesting to note that my patients rarely developed sinus tachycardia, in spite of the presence of fever in 61 per cent of the cases. That rarity, a completely normal electrocardiogram in the acute phase, appeared once in this series, and this incidence is approximately the same as that reported by others (Table I).

TABLE I. ELECTROCARDIOGRAPHIC CHARACTERISTICS OF ACUTE IDIOPATHIC PERICARDITIS (PERCENTAGE INCIDENCE)

	CLASSIC S-T ELEVATION	TACHYCARDIA OVER 100	TRANSIENT AURICULAR FIBRILLATION	NORMAL ECG
31 cases (Soffer)	59	19	13	3
325 cases (from the literature)	63.8	49	—	6

An early wave of enthusiasm for the determination of Q-T_c in diffuse myocardial disease has subsided, tempered by reports that changes in electrical systole in rheumatic fever are erratic[45] and all too often indistinguishable from normal variations.[46] However, a decade of unhurried reflection permits us now to throw away the chaff and utilize this measurement more sagely. It may be seen in Table II that the electrocardiogram in idiopathic pericarditis manifests remarkable consistency as regards the Q-T_c values. The corrected Q-T interval (Q-T_c) was calculated from the modified Bazett formula,

$$Q\text{-}T_c = \frac{\text{Q-T interval}}{\sqrt{\text{cycle length}}}$$

In the presence of either S-T-segment elevation or T-wave inversion, the Q-T_c is normal and remains normal throughout the period of convalescence. Only 3 patients in this group of 31 showed prolongation of the Q-T_c, and the maximum rise was only to 44.5. Indeed, even this isolated maximal elevation reading lasted for only 12 hours and then dropped to 41. The upper limit of normal for

TABLE II. ANALYSIS OF ELECTRICAL SYSTOLE IN IDIOPATHIC PERICARDITIS (31 CASES*)

	NUMBER OF PATIENTS	NUMBER OF ELECTRO-CARDIOGRAMS	AVERAGE Q-T_c	AVERAGE HEART RATE PER MINUTE
S-T-segment elevation	18	21	38.2	78
T-wave inversion	20	27	40.1	86
Normal convalscent ECG	8	8	39.5	70

*Patients who manifested S-T and T-wave changes are listed in both columns.

Q-T_c for all age groups and both sexes in this study is 42.5, based upon criteria established by Kossmann.[47] Of what value is the observation that the Q-T_c is, with rare exception, normal in acute idiopathic pericarditis? In the isolated case it will not serve to distinguish the electrocardiogram of this disease from that of coronary disease,[48] or, as noted above, from that of rheumatic myocarditis.

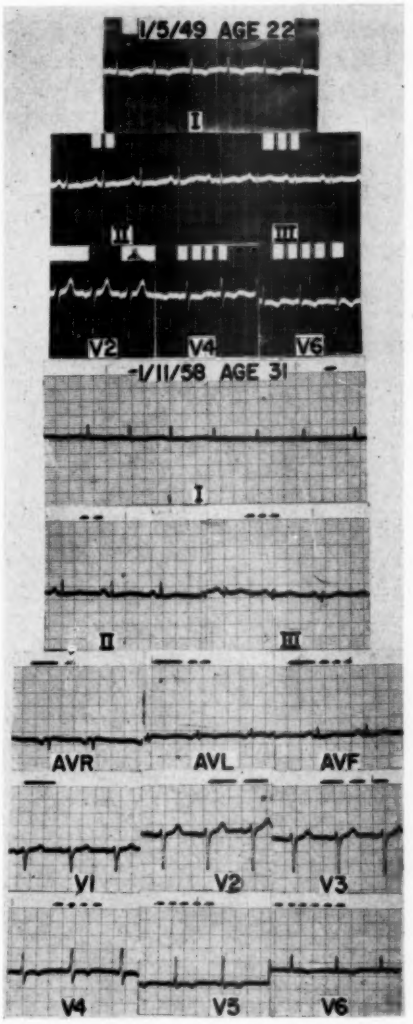

Fig. 1.—Electrocardiograms after acute idiopathic pericarditis which occurred in July, 1948, when the patient was 22 years old (Case 1). Markedly abnormal T waves were present during this 10-year period. Electrocardiograms taken in July and August, 1948, immediately after onset of symptoms manifested classic S-T-segment and T-wave changes of acute pericarditis.

However, the finding of a markedly prolonged Q-T_c has been noted in our laboratory during the "interrupted sequence" of myocardial infarction,[49] and the Q-T_c is prolonged in congestive heart failure.[50,51] In these cases and in instances of myocarditis when this value is unequivocally prolonged, a Q-T_c may serve its masters well as a differential modality, since all of these conditions may closely mimic idiopathic pericarditis.

A NORMAL ELECTROCARDIOGRAM IN THE CONVALESCENT PERIOD

With reversion to a normal electrocardiogram in the convalescent period, the Q-T_c and the heart rate remain approximately the same as they were in the acute phase (Table II).

PERSISTENT ELECTROCARDIOGRAPHIC ABNORMALITIES

Three young men, 22, 29, and 30 years old, manifested abnormalities in the follow-up period in the absence of recurrences of an acute disease process.

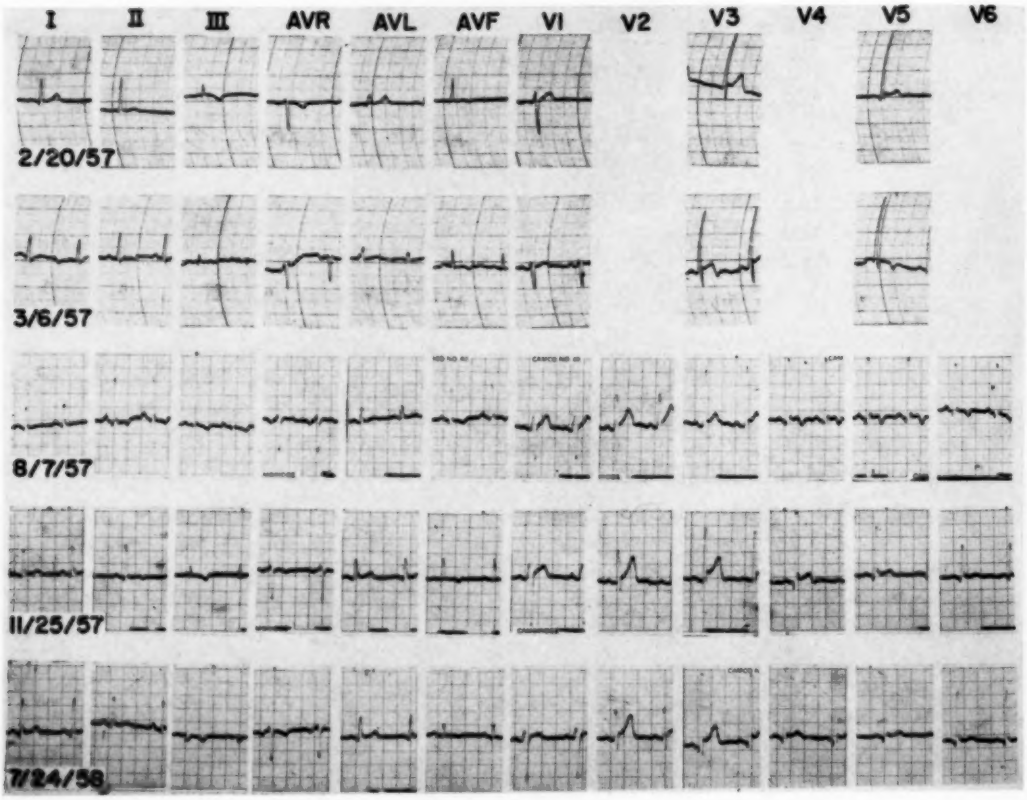

Fig. 2.—Serial electrocardiograms recorded on a 30-year-old man (Case 2) show the appearance, disappearance, and reappearance of S-T-segment elevation during a 17-month period of observation.

CASE 1.—A 22-year-old man experienced substernal pain for a 1-week period in July, 1948. This pain was accentuated with breathing or postural shifts. Nausea, chills, and a fever of 104°F. developed at the end of 7 days, and hospitalization was required. At this time a very loud pericardial friction rub was heard. A sharp drop in hemoglobin to 10 Gm./100 ml. prompted blood transfusion therapy. A chest x-ray film showed cardiomegaly, and a repeated x-ray film 2 weeks after hospitalization showed return of the heart size to normal. The electrocardiogram in the late convalescent phase in early 1949, and another in 1958, are shown in Fig. 1. The patient became free of symptoms in 1948, and he has no known impairment of cardiac and pulmonary functions.

CASE 2.—A 30-year-old attorney was examined because of marked fatigue. Definite S-T-segment elevation prompted serial electrocardiograms, and as demonstrated in Fig. 2, major T-wave and S-T-segment abnormalities were recorded in a 17-month period. During this time the

patient was afebrile, asymptomatic, and a pericardial friction rub was never heard. Determinations of C-reactive protein and sedimentation rate were normal, and his cardiac contour was normal (Fig. 3).

CASE 3.—A 29-year-old man experienced poorly defined epigastric discomfort. An electrocardiogram showed profound abnormality of the S-T segment and T wave. Hospitalization was recommended, and on admission a white blood cell count of 14,000 per cubic millimeter was obtained. No other evidence of cardiac disease has ever been recorded. The patient experienced an asymptomatic and afebrile course in the hospital. His electrocardiograms are shown in Fig. 4, and the electrocardiographic change after exercise is noted in Fig. 5.

Comments.—It has been repeatedly observed that in idiopathic pericarditis the electrocardiogram reverts to normal within a 6-week to 3-month period, and this should usually serve to distinguish idiopathic pericarditis from myocardial infarction. In the later state,[52] as in myocardial ischemia,[48,53] the T waves may persist for long periods of time. The 3 cases recorded above illustrate that this cannot be an infallible rule. Case 1 manifests perhaps the most prolonged period ever recorded of T-wave abnormalities after acute idiopathic pericarditis. It has

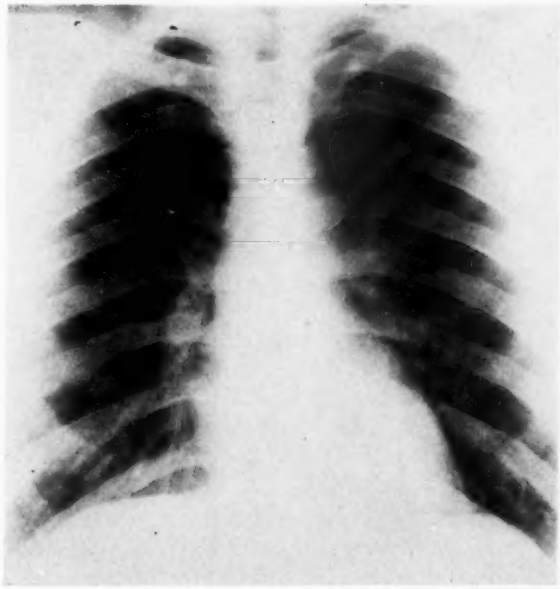

Fig. 3.—Chest x-ray film of Case 2, manifesting normal cardiac contour. This x-ray film was taken at the time of maximum electrocardiographic abnormalities (injury-current pattern) as pictured in Fig. 2.

been stated that in pericarditis of all types, S-T-segment elevation lasts no longer than 12 days.[44] A more recent report, however, documents the presence of an injury-current pattern for at least 3 months.[5] Cases 2 and 3 in this series also demonstrate markedly persistent S-T-segment elevation. In duration of electrocardiographic abnormalities, myocarditis resembles idiopathic pericarditis.[54] Here again, however, infallibility must not be claimed, since abnormalities of very long duration can occur in myocarditis.[55,56]

Cases 2 and 3 demonstrate few clinical stigmata of pericarditis, but other reports point out that this disease may be suspected in the absence of pain and

friction rub, and even if the electrocardiogram is consistently normal (Table I). Case 3 is perhaps in the "twilight zone," suspended between the possibilities of idiopathic pericarditis or coronary disease. Sharp T-wave inversion in the precordial leads is always highly suggestive of atherosclerotic involvement of the heart.[57-59] Of course, epigastric pain can be the presenting complaint of pericarditis,[14] as well as of coronary thrombosis. However, the patient has never

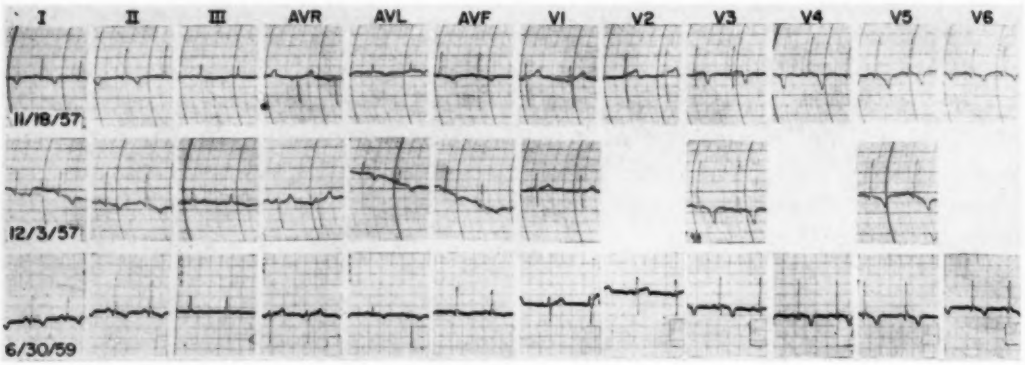

Fig. 4.—Persistent S-T-segment and T-wave abnormalities in a 29-year-old man (Case 3).

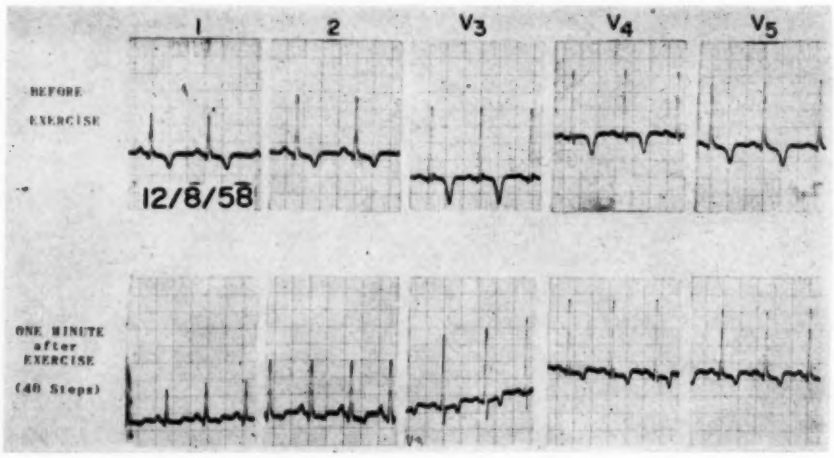

Fig. 5.—After exercise there is a disappearance of the S-T-segment elevation seen in Fig. 4.

TABLE III. ELECTROCARDIOGRAPHIC FINDINGS IN IDIOPATHIC PERICARDITIS, MYOCARDITIS, AND CORONARY DISEASE

	IDIOPATHIC PERICARDITIS	MYOCARDITIS	CORONARY DISEASE
Heart block	0	Yes	Yes
Long Q-T_c	0	Yes	Yes
Intraventricular block	0	Yes	Yes
Wide Q waves	0	Yes	Yes

had abnormal signs or symptoms after strenuous exertion, and after a standard double two-step Master's test his S-T segments returned to the base line (Fig. 5). This response has been observed in the healed stages of idiopathic pericarditis.[60]

Finally, it may be noted that S-T-segment depression may frequently occur in the evolutionary pattern of idiopathic pericarditis. Seven of our cases manifested such depression. It is not surprising, therefore, to note that pericardial calcification in otherwise normal people may produce S-T-segment depression.[61]

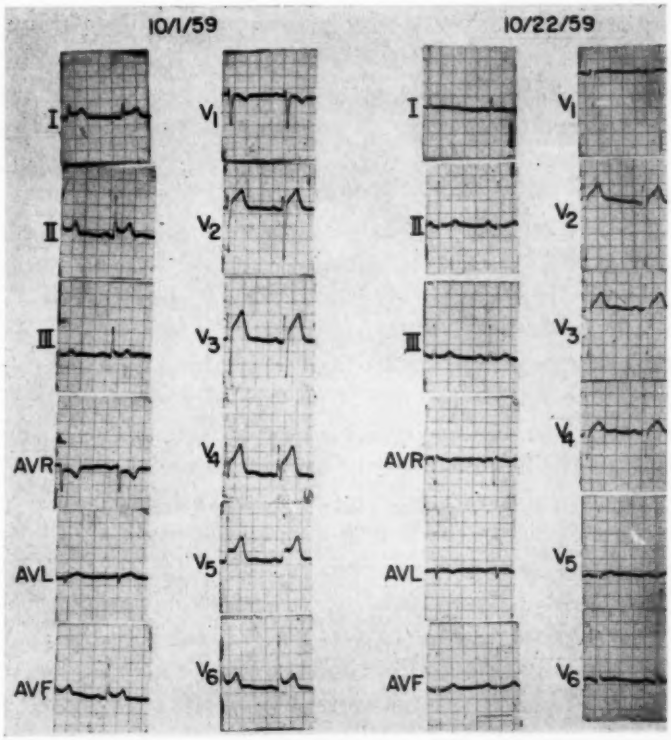

Fig. 6.—S-T-segment elevation with "evolution" toward a normal pattern due to neoplastic involvement of the pericardium.

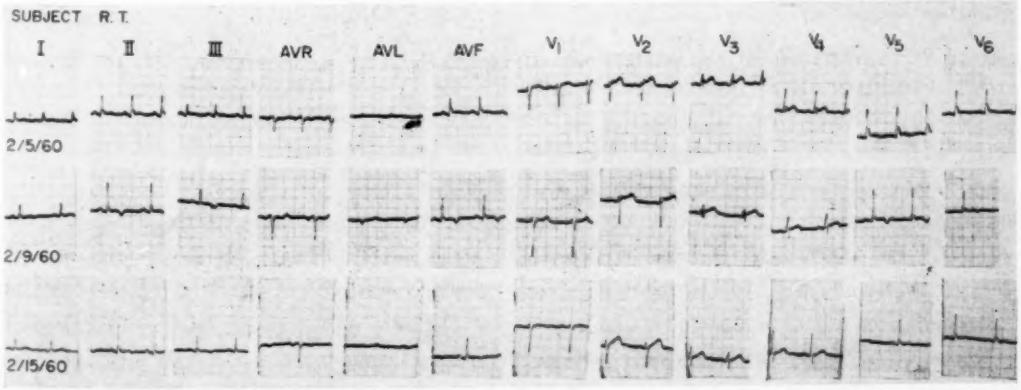

Fig. 7.—Abnormal S-T-segment elevation and T-wave abnormalities due to diabetic acidosis.

DIFFERENTIAL DIAGNOSIS

With some temerity, the author should like to paraphrase a classic aphorism to read, "In electrocardiography, not all that is elevated is pericarditis." The electrocardiogram of a 58-year-old man with S-T elevation suggestive of acute pericarditis is pictured in Fig. 6. The degree of S-T-segment elevation decreased within a reasonable period of time, and the squeezing substernal chest pain disappeared, with improvement in the electrocardiogram. However, a persistent and suspicious retrocardiac shadow prompted thoracotomy, and a bronchogenic carcinoma with parietal pericardial involvement was found. Fig. 7 demonstrates S-T-segment elevation with improvement in a 30-year-old diabetic patient. Acidosis and cellular shifts of potassium and not pericarditis were responsible for the electrocardiographic changes. A comparable electrocardiographic pattern has been seen in this hospital recently in a 33-year-old woman who had experienced a pneumothorax.

Analysis of the 31 cases presented in this series suggests characteristics which may serve to distinguish idiopathic pericarditis from myocarditis or coronary disease (Table III). First- or second-degree heart block is not present in idiopathic pericarditis, but it is often found in the other two clinical states. If the Q-T_e is markedly prolonged, pericarditis is almost certainly absent. Intraventricular block was not found in these patients with pericarditis. Wide Q waves may appear when extensive fibrous replacement occurs in such diseases as "isolated myocarditis"[62] but does not appear in pericarditis. All three entities may demonstrate typical coronary type of T waves.

The limitations of electrocardiography must be considered in every schema of differential diagnosis. Grusin[63] reported profound lability of S-T segments and T waves in the electrocardiograms of normal African subjects. Malnutrition, a prominent factor in Grusin's subjects, was never present in the patients described in this paper. Yet it would be presumptuous to insist that the electrocardiographic contours seen in Cases 2 and 3 are necessarily manifestations of cardiac pathology. An open mind and frequent reappraisals are necessary when, as in these two cases, the diagnosis of idiopathic pericarditis rests predominantly upon electrocardiographic findings.

SUMMARY

Thirty-one cases of idiopathic pericarditis were observed for periods of from 6 months to 10 years. Four patients, or 13 per cent, experienced transient episodes of auricular fibrillation in the acute phase. Electrical systole (Q-T_e) was, with rare exception, normal in the acute, convalescent, and recurrent stages, and heart block was never present. Analysis of these data suggests certain characteristics which may serve to distinguish idiopathic pericarditis from myocarditis or coronary disease. Examples are recorded of electrocardiographic patterns which mimic the acute phase of idiopathic pericarditis. Three young men manifested persistent S-T-segment or T-wave abnormalities for 17 months, 19 months, and 10 years, respectively. These observations contribute to the growing conviction that this so-called "benign" pericarditis may be followed by long-lasting myocardial pathology.

REFERENCES

1. Carmichael, D. B., Sprague, H. B., Wyman, S. M., and Bland, E. F.: Acute Nonspecific Pericarditis, Circulation **3**:321, 1951.
2. Godfrey, J.: Myocardial Involvement in Acute Nonspecific Pericarditis: A Report of Three Cases, Ann. Int. Med. **35**:1336, 1951.
3. Pohl, A. W.: Acute Pericarditis: A Report of Eight Cases in Which the Etiology Was "Nonspecific" or Cryptic, Ann. Int. Med. **32**:935, 1950.
4. McCall, M., and Hertz, A.: Acute Nonspecific Pericarditis, Am. J. Cardiol. **1**:475, 1958.
5. Feder, I. A., Hoffman, J., and Sugar, H.: Acute Primary Pericarditis, Am. J. M. Sc. **220**:144, 1950.
6. Krook, H.: Acute Nonspecific Pericarditis, Acta med. scandinav. **148**:201, 1954.
7. Freilich, J. K.: Acute Nonspecific Pericarditis Complicated by the Development of a Fibrous Pericardium, Ann. Int. Med. **37**:388, 1952.
8. Chapman, D. W., and Overholt, E.: Acute Benign Idiopathic Pericarditis, Arch. Int. Med. **99**:708, 1957.
9. Katz, M., and Jackson, A.: Benign Recurrent Pericarditis, Am. Pract. & Digest Treat. **8**:936, 1957.
10. Gelfand, M. L., and Goodkin, L.: Acute Benign Nonspecific Pericarditis Without a Pericardial Friction Rub, Ann. Int. Med. **45**:490, 1956.
11. Logue, R. B., and Wendkos, M. H.: Acute Pericarditis of Benign Type, Am. Heart J. **36**:587, 1948.
12. Witherbee, H. R., and Pearce, M. L.: Shock and Acute Abdominal Symptoms Complicating Acute Idiopathic Pericarditis, Ann. Int. Med. **49**:876, 1958.
13. Levy, R. L., and Patterson, M. C.: Acute Serofibrinous Pericarditis of Undetermined Cause, Am. J. Med. **8**:35, 1950.
14. Powers, P. P., Read, J. L., and Porter, R. R.: Acute Idiopathic Pericarditis Simulating Acute Abdominal Disease, J.A.M.A. **157**:224, 1955.
15. Singer, M. M.: Acute Idiopathic Pericarditis, Am. Heart J. **58**:568, 1959.
16. Evans, E.: Acute Nonspecific Benign Pericarditis, J.A.M.A. **143**:954, 1950.
17. Zivitz, N., and Oshlag, J. A.: Eosinophilic Pleural Effusion and Pericarditis With Effusion in an Allergic Patient, J. Allergy **20**:136, 1949.
18. Goyette, E. M.: Acute Idiopathic Pericarditis, Ann. Int. Med. **39**:1032, 1953.
19. Parker, R. C., and Cooper, H. R.: Acute Idiopathic Pericarditis, J.A.M.A. **147**:835, 1951.
20. Sodeman, W. A., and Smith, R. H.: A Re-Evaluation of the Diagnostic Criteria for Acute Pericarditis, Am. J. M. Sc. **235**:672, 1958.
21. Pomerance, M., Perchuk, E., and Hoffman, J. B.: A Fatal Case of Idiopathic Pericarditis, New York J. Med. **52**:95, 1952.
22. Scherl, N. D.: Acute Nonspecific Pericarditis: A Survey of the Literature and A Study of Thirty Additional Cases, J. Mt. Sinai Hosp. **23**:293, 1956.
23. Nay, R. M., and Boyer, N. H.: Acute Pericarditis in Young Adults, Am. Heart J. **32**:222, 1946.
24. Porter, W. B., Clark, O., and Porter, R. R.: Nonspecific Benign Pericarditis, J.A.M.A. **144**:749, 1950.
25. McCuiston, C. F., and Moser, K. M.: Studies in Pericarditis, Am. J. Cardiol. **4**:42, 1959.
26. Movitt, E. R., Lennette, E. H., Mangum, J. F., Berk, M., and Bowman, M. S.: Acute Benign Pericarditis: Report of Two Cases Associated With Group A and Group B Coxsackie Viruses, New England J. Med. **258**:1082, 1958.
27. Weinstein, S. B.: Acute Benign Pericarditis Associated With Coxsackie Virus Group B Type 5, New England, J. Med. **257**:265, 1957.
28. Herrmann, G. R., Marchand, E. J., Greer, H., and Hejtmancik, M. R.: Pericarditis—Clinical and Laboratory Data of 130 Cases, Am. Heart J. **43**:641, 1952.
29. Barnes, A. R., and Burchell, H. B.: Acute Pericarditis Simulating Acute Coronary Occlusion: A Report of Fourteen Cases, Am. Heart J. **23**:247, 1942.
30. Talmage, W. O.: Acute Benign Pericarditis, Am. Heart J. **29**:623, 1945.
31. Friedman, S., Ash, R., Harris, T. N., and Lee, H. F.: Acute Benign Pericarditis in Childhood. Comparisons With Rheumatic Pericarditis and Therapeutic Effects of ACTH and Cortisone, Pediatrics **9**:551, 1952.
32. Tomlin, C. E., Logue, R. B., and Hurst, J. W.: Recurrent Nature of Acute Benign Pericarditis, J.A.M.A. **149**:1215, 1952.
33. Nathan, D. A., and Dathe, R. A.: Pericarditis With Effusion Following Infections of the Upper Respiratory Tract, Am. Heart J. **31**:115, 1946.
34. Dressler, W.: Idiopathic Recurrent Pericarditis, Am. J. Med. **18**:591, 1955.
35. Rosenow, O. F., and Cross, C. J.: Acute Benign Pericarditis, Arch. Int. Med. **87**:795, 1951.
36. Marois, A., and Marcoux, G.: Acute Benign Pericarditis, Canad. M. A. J. **75**:834, 1956.
37. Wolff, L.: Acute Pericarditis With Special Reference to Changes in Heart Size, New England J. Med. **229**:423, 1943.
38. Nathan, D. A., and Dathe, R. A.: Pericarditis With Effusion Following Infections of the Upper Respiratory Tract, Am. Heart J. **31**:115, 1946.

39. Coffen, C. W., and Scarf, M.: Acute Pericarditis Simulating Coronary Artery Occlusion, Am. Heart J. **32**:515, 1946.
40. Zinsser, H. F., Balkemore, W. S., Kirby, C. K., and Johnson, J.: Invalidism Due to Recurrent Idiopathic Pericarditis With Recovery After Pericardiectomy, J.A.M.A. **171**:274, 1959.
41. Barnes, A. R., and Mann, F. C.: Electrocardiographic Changes Following Ligation of the Coronary Arteries of the Dog, Am. Heart J. **7**:477, 1932.
42. Burchell, H. B., Barnes, A. R., and Mann, F. C.: The Electrocardiographic Picture of Experimental Localized Pericarditis, Am. Heart J. **18**:133, 1939.
43. VanderVeer, J. B., and Norris, R. F.: The Electrocardiographic Changes in Acute Pericarditis, Am. Heart J. **14**:31, 1937.
44. Bellet, S., and McMillan, T. M.: Electrocardiographic Patterns in Acute Pericarditis, Arch. Int. Med. **61**:381, 1938.
45. Rushner, R. F.: Cardiac Diagnosis: A Physiologic Approach, Philadelphia, 1955, W. B. Saunders Company.
46. Craige, E., Alimurung, M. M., Bland, E. F., and Massell, B. F.: The Q-T Interval in Rheumatic Fever, Circulation **1**:1338, 1950.
47. Kossmann, C. E.: The Normal Electrocardiogram, Circulation **8**:920, 1953.
48. Schlant, R. C., Levine, H. D., and Bailey, C. C.: "Isolated" T-Wave Negativity in the "Ischemic Phase" of Myocardial Infarction in Man, Circulation **10**:829, 1954.
49. Soffer, A.: Significance of Serial "K" Determinations and of Certain Premature Contractions in Acute Myocardial Injury, Am. J. M. Sc. **237**:87, 1959.
50. Tung, C. L.: The Duration of Electrical Systole (Q-T Interval) in Cases of Massive Pericardial Effusion, Am. Heart J. **22**:35, 1941.
51. Cheer, S. N., and Dieuaide, F. R.: Studies on the Electrical Systole "Q-T" Interval of the Heart, J. Clin. Invest. **10**:889, 1931.
52. Gittler, A., Schack, J. A., and Vesell, H.: The Electrocardiogram One Year After Acute Myocardial Infarction, Am. Heart J. **51**:246, 1956.
53. Mathewson, F. A. L., and Varnam, G. S.: Abnormal Electrocardiograms in Apparently Healthy People. II. The Electrocardiogram in the Diagnosis of Subclinical Myocardial Disease: Serial Records of Thirty-Two People, Circulation **21**:204, 1960.
54. De la Chapelle, C. F., and Kossmann, C. E.: Myocarditis, Circulation **10**:747, 1954.
55. Silber, E. N.: Respiratory Viruses and Heart Disease, Ann. Int. Med. **48**:228, 1958.
56. Sayers, E. G.: Diphtheritic Myocarditis With Permanent Heart Damage, Ann. Int. Med. **48**:146, 1958.
57. Pruitt, R. D., Klakey, C. H., and Chapin, L. E.: Certain Clinical States and Pathologic Changes Associated With Deeply Inverted T Waves in the Precordial Electrocardiogram, Circulation **11**:517, 1955.
58. Cutts, F. B., Merlino, F., and Easton, F. W.: Chest Pain With Inverted T Waves Predominantly in Precordial Leads as the Only Electrocardiographic Abnormality, Circulation **16**:599, 1957.
59. Myers, G. B.: Other QRS-T Patterns That May Be Mistaken for Myocardial Infarction, Circulation **2**:75, 1950.
60. McGuire, J., Helm, R. A., Iglauer, A., Scott, R. C., Kotte, H. K., and Felson, B.: Nonspecific Pericarditis and Myocardial Infarction, Circulation **14**:874, 1956.
61. Marriott, H. J. L.: Coronary Mimicry, Normal Variants and Physiologic, Pharmacologic, and Pathologic Influences That Simulate Coronary Patterns in the Electrocardiogram, Ann. Int. Med. **52**:411, 1960.
62. Keith, J. D., Rowe, R. D., and Vlad, P.: Heart Disease in Infancy and Childhood, New York, 1958, The Macmillan Company.
63. Grusin, H.: Peculiarities of the Africans' Electrocardiogram and the Changes Observed in Serial Studies, Circulation **9**:860, 1954.

Division of the P Wave by the Sondergaard Suture

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Because of the frequent finding of bifid P waves after repair of atrial septal defects by the Sondergaard method, the electrocardiograms of 18 consecutive patients operated on by this technique were reviewed.

MATERIAL AND METHODS

The patients ranged in age from 9 to 49 years; the majority were adults. Cardiac catheterization was performed before operation in all but 3 patients, and a normal pulmonary vascular resistance and a large left-to-right shunt were found in 12 cases. Two patients had a moderate increase in pulmonary vascular resistance, and another had a high resistance with cyanosis and bidirectional shunts. An ostium secundum defect was found in each case and was closed by a circumferential suture in the plane of the atrial septum, passing through the lower rim of the septum between the atrioventricular valves.[1,2] Closure was incomplete in 2 patients (H. B. and L. J.). Postoperative catheterization was performed in these and in 4 other cases. There was evidence of slight mitral stenosis in 1 patient (B. H.).

Routine 12-lead electrocardiograms taken with a Cambridge direct-writing instrument were analyzed. By means of a hand lens, intervals were measured to the nearest 0.01 second and 0.25 millimeter. The axes of the peaks of the P wave were calculated in the frontal plane using the standard limb leads, and in the horizontal plane from Leads V_1 and V_6. Postoperative electrocardiograms were taken in the second week, soon after removal of the dressings. In 9 patients, electrocardiograms were taken in the first few days after operation because of arrhythmia.

RESULTS

A supraventricular arrhythmia was identified postoperatively in 10 patients, and 5 showed two or three different disturbances. The arrhythmias recorded were: atrial fibrillation (2), atrial flutter (2), atrial tachycardia (2), nodal tachycardia (2), nodal rhythm (4), prolonged P-R interval (2), 2:1 atrioventricular block (1), and complete heart block (1). Normal sinus rhythm returned in 6 patients before they were discharged from the hospital, but in 4 patients the arrhythmia persisted.

Electrocardiograms which showed sinus rhythm before and after operation were available in 14 patients. The P-R interval was between 0.13 and 0.20 sec.

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TABLE I. CHANGES IN THE P-R INTERVAL AND P WAVE AFTER OPERATION

PATIENT	P-R INTERVAL (SEC.)			P WAVE (SEC.)			TIMING OF P-WAVE PEAKS (SEC.)					
							PREOPERATIVE			POSTOPERATIVE		
	PREOP.	POSTOP.	DIFFERENCE	PREOP.	POSTOP.	DIFFERENCE	FIRST PEAK	SECOND PEAK	INTERVAL	FIRST PEAK	SECOND PEAK	INTERVAL
E. B	0.16	0.16	0	0.11	0.12	+0.01	0.06	—	—	0.02	0.07	0.05
H. B.	0.13	0.22	+0.09	0.09	0.12	+0.03	0.04	—	—	0.04	0.09	0.05
D. C.	0.18	0.18	0	0.11	0.12	+0.01	0.07	—	—	0.04	0.09	0.05
M. C.	0.17	0.20	+0.03	0.09	0.12	+0.03	0.06	—	—	0.04	0.09	0.05
O. D.	0.20	0.20	0	0.10	0.12	+0.02	0.06	—	—	0.06	0.10	0.04
D. D.	0.18	0.20	+0.02	0.11	0.13	+0.02	0.06	—	—	0.04	0.10	0.06
M. G.	0.19	0.20	+0.01	0.09	0.12	+0.03	0.06	—	—	—	0.09	—
B. H.	0.17	0.17	0	0.11	0.11	0	0.06	—	—	0.04	0.08	0.04
L. J.	0.17	0.17	0	0.11	0.12	+0 01	0.06	—	—	0.04	0.08	0.04
O. L.	0.20	0.20	0	0.13	0.14	+0.01	0.06	0.10	0.04	0.04	0.12	0.08
B. M.	0.16	0.16	0	0.12	0.14	+0.02	0.04	0.08	0.04	0.04	0.12	0.08
L. O.	0.14	0.22	+0.08	0.10	0.12	+0.02	0.04	—	—	0.04	0.10	0.06
M. O.	0.18	0.18	0	0.12	0.12	0	0.06	—	—	0.04	0.10	0.06
H. R.	0.16	0.16	0	0.12	0.12	0	0.04	0.08	0.04	0.04	0.08	0.04
Mean	0.17	0.19	+0.02	0.11	0.12	+0.01	0.06	0.09	0.04	0.04	0.09	0.05

before operation. In most patients there was no change after operation, but 2 showed considerable prolongation of the P-R interval to 0.22 sec. (L.O., Fig. 1), and in 3 others there were minor changes (Table I).

Before operation the width of the P wave was between 0.09 and 0.13 sec. The P axis was directed to the left, inferiorly, and, in most cases, anteriorly (Fig. 2), producing positive deflections in all leads except Lead V_R and sometimes Leads V_L or III, and a diphasic wave with a late negative component in Lead V_1. The peak of P was usually 0.06 sec. after the onset (Table I), and averaged 1½ mm. in height, the largest being 3 mm. In 3 patients the late negative deflection in Lead V_1 coincided with a small second peak in other leads (O.L., Fig. 1). The axis of this late component was directed to the left, inferiorly, and posteriorly (Fig. 2), and the interval between the peaks was 0.04 sec.

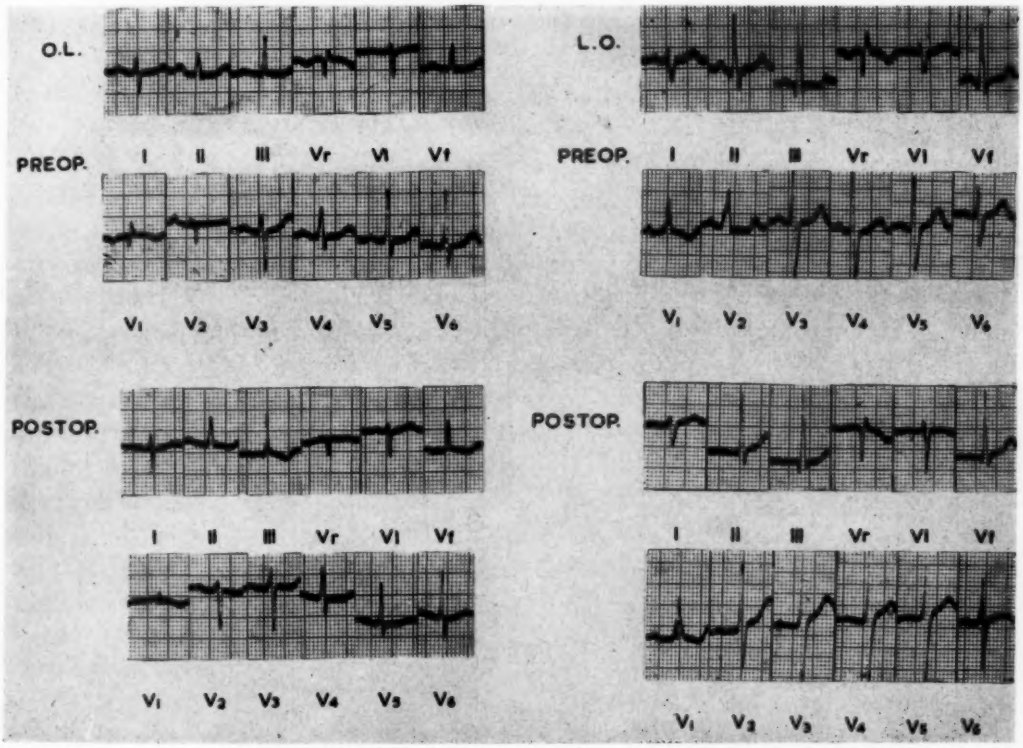

Fig. 1.—The electrocardiograms recorded before and after operation in 2 patients with atrial septal defect.

Postoperatively, 11 patients showed prolongation of the P wave, which was between 0.11 and 0.14 sec. in duration. The late posterior component was more prominent, and bifid P waves were found in all but 1 patient who had a wide P wave with a late peak (Table I). The first peak was 0.04 sec. after the onset of P and averaged ¾ mm. in amplitude. The axis of this component was usually similar to that of the P wave before operation (Fig. 2).

The second peak also averaged ¾ mm. in height, but its axis was posterior and usually to the left and upward (Fig. 2), so that bifid P waves were well

seen in Leads I and V_L. The interval between the peaks varied from 0.04 to 0.08 sec. In 2 patients with bifid P waves before operation the interval between the peaks increased by 0.04 sec. (O.L., Fig. 1). In the other patient the interval did not change, but the axis of the second peak became directed posteriorly and upward.

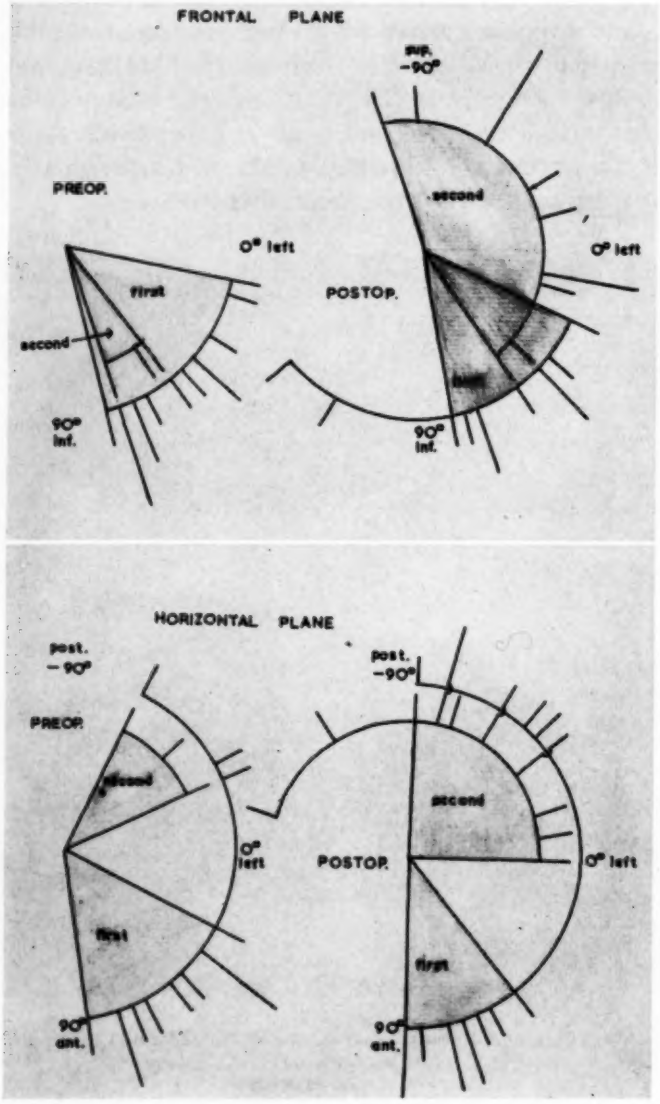

Fig. 2.—The axes of the first and second peaks of the P wave before and after operation in 14 patients with atrial septal defect.

DISCUSSION

Studies of the electrical activity of the atrium by both scalar[3,4] and vector[5,6] methods have been reported. The left atrium is activated later than the right, but in normal subjects there is considerable overlap between the two components.

In the vectorcardiogram the P loop is directed to the left, inferiorly, and forward.[5,6] The later parts of the loop are relatively posterior, producing a small negative deflection in Lead V_1 and occasionally a second peak in other leads. Left atrial hypertrophy accentuates this late component so that there is a wide negative deflection in Lead V_1,[7] and more obviously bifid P waves elsewhere, with an interval of more than 0.04 sec. between the peaks.[3] These changes prolong the P wave at the expense of the P-R segment. Right atrial hypertrophy augments the early part of the P wave and tends to prolong the P-R interval.[4]

In atrial septal defect of the ostium secundum type the P wave usually indicates a minor degree of right atrial hypertrophy or shows a normal pattern. In a minority of patients there are changes which suggest left atrial hypertrophy.[8-10] Most patients in the present study had normal P waves before operation. The small second peak found in 3 patients is not necessarily evidence of left atrial disease.[3] After operation all patients showed accentuation of the late component of the P wave, producing a second peak, with its axis usually directed to the left, posteriorly, and upward. In most cases the P wave was widened and the interval between the peaks exceeded 0.04 sec.

A shift of the P axis to the left has been reported in the majority of patients after closure of an atrial septal defect by other methods.[8] Elevation of the left atrial pressure associated with increased filling of a hypoplastic left ventricle may be responsible, but a raised left atrial pressure is rarely found after operation unless there is mitral valvular disease.[11] The patient with mitral stenosis in the present study showed no distinctive features.

An alternative explanation for the P-wave changes reported here is the production of interatrial block as a result of damage to the tissue of the atrial septum by the Sondergaard suture. The consequent delay in activation of the left atrium prolongs the P wave[12] and separates the right and left atrial components. The first component is smaller than the original P wave but shows little change in orientation, suggesting that the preoperative P wave was dominated by right atrial activity. The second component is produced by left atrial activation, which is no longer masked by simultaneous right atrial depolarization. The bifid P waves which are found naturally in some patients with atrial septal defect may also be produced by interatrial block.[9]

The high incidence of arrhythmia after operation suggests that the atrioventricular node or related parts of the conduction system may be damaged by the suture. In most patients no serious results follow these changes, which are often transient, although treatment with digitalis may be needed. Persistent complete heart block, however, is a potential hazard.

SUMMARY AND CONCLUSIONS

The changes in the P wave of the electrocardiogram after repair of atrial septal defect by the Sondergaard method of circumferential suture in 18 patients are reviewed. In every case the P wave was divided into two components after the operation, presumably as a result of interatrial block. Supraventricular arrhythmias were frequent. These changes in conduction did not interfere with the success of the operation.

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REFERENCES

1. Sondergaard, T.: Closure of Atrial Septal Defects; Report of Three Cases, Acta chir. scandinav. **107**:493, 1954.
2. Björk, V. O., Crafoord, C., Jonsson, B., Kjellberg, S. R., and Rudhe, U.: Atrial Septal Defects; A New Surgical Approach and Diagnostic Aspects, Acta chir. scandinav. **107**:499, 1954.
3. Thomas, P., and Dejong, D.: The P Wave in the Electrocardiogram in the Diagnosis of Heart Disease, Brit. Heart J. **16**:241, 1954.
4. Macruz, R., Perloff, J. K., and Case, R. B.: A Method for the Electrocardiographic Recognition of Atrial Enlargement, Circulation **17**:882, 1958.
5. Wenger, R., Doneff, D., and Hupka, K.: Vectorkardiographische Untersuchungen vor und nach Operationen wegen Mitralstenose, Verhandl. Deutsch. Gesellsch. Kreislaufforsch. **20**:149, 1954.
6. Sano, T., Hellerstein, H. K., and Vayda, E.: P Vector Loop in Health and Disease as Studied by the Technique of Electrical Dissection of the Vectorcardiogram (Differential Vectorcardiography), Am. Heart J. **53**:854, 1957.
7. Dines, D. E., and Parkin, T. W.: Some Observations on P-Wave Morphology in Precordial Lead V_1 in Patients With Elevated Left Atrial Pressures and Left Atrial Enlargement, Proc. Staff Meet. Mayo Clin. **34**:401, 1959.
8. Martins de Oliveira, J., and Zimmerman, H. A.: The Electrocardiogram in Interatrial Septal Defect and Its Correlation With Hemodynamics, Am. Heart J. **55**:369, 1958.
9. Cabrera, E., Acosta, A. R., and Dräyer, A.: Correlacion electrocardiografica hemodinamica de la communicacion interauricular, Arch. Inst. cardiol. Mexico **28**:537, 1958.
10. Toscano-Barboza, E., Brandenburg, R. O., and Swan, H. J. C.: Atrial Septal Defect: The Electrocardiogram and Its Hemodynamic Correlation in 100 Proved Cases, Am. J. Cardiol. **2**:698, 1958.
11. Pemberton, A. H., Kirklin, J. W., and Wood, E. H.: Interatrial-Pressure Relationships After Closure of Atrial Septal Defects in Man, Circulation **15**:568, 1957.
12. Abildskov, J. A.: The Atrial Complex of the Electrocardiogram, Am. Heart J. **57**:930, 1959.

Experimental and Laboratory Reports

The Hemodynamic Determinants of the Rate of Change in Pressure in the Left Ventricle During Isometric Contraction

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The ability of the myocardium to alter its rate of contraction and, consequently, the rate of change in pressure in the ventricle is one of its most important properties. It is this ability which allows the period of isometric contraction to remain essentially constant, even though the diastolic pressure in the aorta or pulmonary artery may change remarkably. If the rate of contraction could not be adjusted, the period of isometric contraction would vary as does the diastolic pressure in the aorta. An increase in aortic diastolic pressure from 60 to 120 mm. Hg would double the period of isometric contraction, and the ejection phase would be proportionately reduced if the remainder of the cardiac cycle remained constant. The velocity of ejection is in major part a function of the difference in instantaneous pressure between the ventricle and its adjacent artery. This difference is largely a function of the slope of the ventricular pressure pulse. It is therefore apparent that the rate of increase in pressure within the ventricle, reflected in the slope of the ventricular pressure pulse, is a primary factor in the ability of the heart to increase the velocity of ejection when the stroke volume is increased or the ejection period is decreased, as in tachycardia.

The importance of this property of the heart muscle was recognized very early in the developments of modern cardiac physiology. Frank[1] included the rate of change in pressure along with the maximal pressure attained in his analysis of the frog ventricle during completely isometric contractions. Similarly, Wiggers,[2] in a study of the mammalian ventricle, noted that as the initial (end-diastolic)

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intraventricular pressure increased, so did the steepness of the ascending limb of the ventricular pressure pulse. Starling[3] also emphasized the importance of the rate of change in pressure as a fundamental property of the heart muscle, and, indeed, based his conclusion that stimulation of the vagus nerve decreased the contractility of the ventricular muscle upon this aspect of contraction. "The slow rate of rise of the pressure shows that the effect of the vagus is not confined to altering the rhythm, as determined by the pacemaker, but is a direct one on the processes of the ventricular muscle itself."

Since these early investigations, frequent qualitative estimates as to changes in ventricular contractility have been made on the basis of alterations in the rate of change in pressure. Recently, Rushmer[4] included this function among several others to be considered in making a qualitative estimate of change in ventricular function in the adaptation of the circulation to stress.

In view of this long-standing awareness of the importance of the rate function of ventricular contraction, it is surprising that there have been little or no quantitative data reported as to the relationship of the rate of change in pressure to other fundamental parameters. This investigation was designed to test the hypothesis that the rate of change in pressure could be quantitatively related to the known determinants of ventricular performance, notably, its end-diastolic volume (or fiber length) and its physiologic condition (contractility). We will arbitrarily define contractility for the purpose of this investigation as the maximum tension developed during contraction per unit initial fiber stretch or displacement from resting length.

MATERIAL AND METHODS

The data presented in Table I were derived from 108 experimental conditions in 5 consecutive successfully completed experiments on as many dogs. These results are entirely representative of the findings in experiments upon many other dogs.

The animals were anesthetized with intravenous pentobarbital sodium and morphine sulfate. Thoracotomy was accomplished by means of an electrocautery technique. The trachea was intubated, and respiration adequately maintained by the use of a piston-driven respirator. Aortic pressure was measured through a metal cannula introduced through a brachiocephalic artery to the ascending aorta. Its position was verified by direct palpation. The phasic pressure was sensed by a Statham P23d strain-gauge manometer and was recorded photographically from a multichannel oscilloscopic recorder.* The left ventricular pressure was recorded by a similar system, utilizing a 20-gauge needle directly into the ventricle. The needle was attached to the strain gauge by a short metal adaptor. The over-all response of the needle–cannula–strain gauge and recorder was flat to sinusoidal pressure to beyond 80 c.p.s.

An estimate of the ventricular stretch was obtained by utilizing both the end-diastolic pressure and the end-diastolic circumference of the left ventricle. Changes in the circumference were measured by a variable-resistance gauge described by Rushmer.[6] This gauge consisted of a very narrow thin-walled rubber tube filled with mercury. Alterations in the length of the tubing induced changes in the resistance of the column of mercury which were measured from the imbalance induced in a Wheatstone bridge. Deviation of the circumference record at the end of diastole from an arbitrary base line was plotted against the simultaneously recorded end-diastolic pressure of the ventricle for each of the observations made during the control period. The resulting straight-line graph was adjusted to make the intercept of the regression of the circumference on pressure

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equal zero. The deflections of the circumference gauge were then expressed in terms of the observed corresponding pressure, i.e., X mm. Hg of circumference record equal Y mm. Hg. In this way, changes in circumference could be compared in all dogs. In essence, then, our parameter of ventricular end-diastolic stretch is the ventricular end-diastolic pressure corrected for changes in distensibility in the subsequent conditions of the experiment. This initial assumption was that the distensibility in all dogs was essentially the same at the time of calibration. Since the conditions were essentially identical, this assumption seemed justifiable.

Changes in myocardial contractility were measured by the use of a Walton-Brodie[7] strain-gauge arch sutured to the anterior wall of the left ventricle. Since it is impractical to calibrate this instrument directly in situ, it was assumed that during the control conditions the contractility of the left ventricle at equivalent filling pressures was the same in all dogs. The measured deflection of the record from the strain-gauge arch when the end-diastolic pressure of the left ventricle was 10 mm. Hg was taken as 100 per cent. Subsequent measurements of the output from the strain-gauge arch were then expressed as a percentage of this arbitrarily selected standard condition. All calibrations were made immediately after thoracotomy, prior to administration of any drugs except the anesthetics. It was recognized that, almost certainly, differences in contractility from dog to dog existed. However, since the error would not systematically affect the analysis, it was accepted.

The slopes of the ventricular pressure were computed electrically, by means of an R-C differentiating circuit,* the output of which was proportional to the first time derivative of a sine wave from 1 to 80 c.p.s. This frequency response was tested both electrically and by a sinusoidal pressure wave generated mechanically. The resulting record was calibrated as millimeters of mercury per second by measuring the tangent, graphically constructed, to the anacrotic slope of the ventricular pressure curve of 10 consecutive beats during the control period and relating the mean of these measurements to the mean peak of the simultaneously recorded time derivative of ventricular pressure. From this derivative the slope of the pressure pulse could be determined for any instant in the cardiac cycle. However, the only measurements made for this experiment were of the maximal slope of the isometric contraction portion of the ventricular pressure curve during each experimental condition. The accuracy of the measurements of the slope during tachycardia and under rapidly changing conditions is far greater with the use of the differentiator than by graphic analysis.

All experiments followed the same protocol. After the gauges were positioned and balanced, a large-bore cannula was tied in place into either the right or left atrium. This cannula led to a large electrically heated reservoir of blood taken from donor animals. The pericardium was left open, and all nervous control to the heart was intact. The reservoir was first lowered, inducing an acute depletion of blood volume and a markedly reduced ventricular volume. The reservoir was then raised stepwise until the ventricle was grossly distended, and next was lowered stepwise back to the initial level. At each level of the reservoir, time for equilibration was allowed, and then all parameters were simultaneously recorded at a chart speed of either 150 or 200 mm. per second. The initial series of observations was carried out without drugs (except anesthesia) and is recorded as "control observations" in Table I. Next, a slow infusion of epinephrine was begun at a constant rate intended to induce a slight alteration in myocardial function as estimated by changes in aortic pressure, heart rate, etc. Once a steady state was achieved, the drip was maintained at a constant rate, and stepwise variations in ventricular volume were induced by hemorrhage and infusion as outlined above. Recordings were made at each level of the reservoir, after time for stablization. The third phase of the experiment was designed to induce a marked increase in systemic vascular resistance and, thereby, an increase in ventricular pressure without directly induced changes in ventricular contractility. Methoxamine[8] was therefore given in dosage sufficient to bring about an increase of approximately 25 per cent in systolic pressure at the basal level of the atrial reservoir. After this had been achieved by an initial rapid infusion, a very slow drip of diluted methoxamine was maintained to ensure a steady state of effect of the drug. The atrial reservoir was again raised and lowered in stepwise fashion and recordings were made in the manner described.

*Made by Electronics for Medicine, Inc., White Plains, N. Y.

TABLE I

DOG NUMBER	EXPERIMENTAL CONDITIONS		LEFT VENTRICULAR END-DIASTOLIC STRETCH INDEX	VENTRICULAR PRESSURE (MM. Hg)		VENTRICULAR PRESSURE AREA (MM. Hg × SEC.) (SYSTOLIC)	MAXIMUM SLOPE OF ISOMETRIC CONTRACTION (MM. Hg/SEC.)	CONTRACTILITY INDEX–STRAIN-GAUGE ARCH (PER CENT OF CONTROL)	AORTIC PRESSURE (MM. Hg) S/D	MAXIMUM CONTRACTILE TENSION INDEX (STRETCH × CONTRACTILITY)
				SYSTOLIC	END-DIASTOLIC					
I	Control	1	6.7	119	6.9	18.1	3,060	—	119/65	—
		2	15.9	130	16.1	23.0	2,900	111.15	130/59	1,767.29
		3	21.5	134	24.2	24.6	3,790	88.18	140/64	1,895.87
		4	21.5	134	24.2	24.5	3,870	90.40	134/54	1,943.60
		5	15.3	126	14.5	22.7	3,790	104.48	128/45	1,598.54
		6	9.7	111	10.9	17.8	3,385	100.03	113/40	970.29
I	Epinephrine	1	10.0	122	9.7	18.3	4,350	128.19	122/45	1,281.90
		2	14.3	124	14.5	21.3	3,870	111.15	124/44	1,589.45
		3	20.2	139	22.6	23.8	4,830	108.93	139/51	2,178.60
		4	22.5	137	27.4	24.7	4,190	102.26	137/50	2,300.85
		5	24.0	134	29.9	24.7	3,545	98.55	134/48	2,365.20
		6	20.5	133	25.4	23.5	3,785	100.78	133/46	2,065.99
		7	13.8	132	15.7	20.9	3,545	108.93	132/42	1,503.23
I	Methoxamine	1	12.3	106	10.9	19.5	2,232	76.32	105/34	938.74
		2	12.8	103	12.1	20.6	1,754	66.69	106/40	853.63
		3	16.4	120	19.4	28.0	1,674	63.73	121/56	1,045.17
		4	21.0	135	24.6	31.1	1,834	54.83	137/66	1,151.43
		5	11.8	119	12.9	23.7	2,312	72.62	116/61	856.92
		6	8.7	107	8.90	21.1	2,630	82.99	110/56	722.01
II	Control	1	6.8	110	6.5	14.6	2,745	141.29	109/80	1,001.57
		2	7.8	102	7.3	15.5	2,173.1	118.86	101/71	927.11
		3	8.9	111	8.5	16.9	3,888.7	125.32	111/60	1,115.35
		4	9.8	89.5	9.5	15.7	2,630	100.13	84/48	981.27
		5	14.1	107	13.7	19.8	2,859	84.63	98/57	1,193.28
		6	9.2	94	9.5	15.2	2,401.8	113.05	92/55	1,040.06
		7	7.6	83	8.0	12.2	2,058.7	125.32	82/51.5	952.43
		8	6.6	70	6.9	10.6	1,601.2	106.59	79/42	703.49
II	Epinephrine	1	5.7	66	6.4	—	2,058.7	87.86	66/34	500.80
		2	7.7	86	8.4	—	2,058.7	87.86	86/48	676.52
		3	11.3	108	11.4	—	3,088.1	106.59	108/68	1,204.47
		4	21.0	157	16	—	4,575	100.13	164/103	2,100.63
		5	11.7	115	10.6	—	3,888.7	100.13	114/77	1,171.52
		6	7.8	81	7.6	—	1,830	122.09	81/54	952.30
		7	7.1	69	8.7	—	1,830	106.59	69/47	756.79

II	Methoxamine	1	7.6	58	8	—	686.2	43.93	58/37	333.87
		2	8.3	50.2	7.6	—	457.5	40.70	51/36	337.81
		3	9.3	71.4	8.7	—	915.0	50.39	75/53	468.63
		4	8.8	62.8	8.4	—	686.2	50.39	66/47	443.43
		5	26.2	136.5	16	—	2,058.7	43.93	140/99	1,150.97
		6	12.2	86.3	10.6	—	1,258.1	50.39	90/61	614.76
		7	7.4	52.5	6.8	—	686.2	43.93	55/41	325.08
		8	6.9	47.1	6.1	—	571.8	50.39	50/37	347.69
III	Control	1	8.1	66	9	13.58	1,695	126.73	66/43	1,026.51
		2	6.8	63	7	9.60	1,864	106.72	64/32	725.70
		3	9.1	87	9	14.8	2,710	100.05	82/43	910.46
		4	14.5	98	15	18.2	2,795	93.38	94/47	1,354.01
		5	16.8	106	16	21.1	3,050	103.39	103/59	1,736.95
		6	7.5	70	7	12.9	1,780	100.05	70/41	750.38
		7	5.5	60	6	9.5	1,864	93.38	60/33	513.90
III	Epinephrine	1	6.5	72	8	—	2,205	110.06	72/42	715.39
		2	9.5	85	10	—	2,710	130.07	85/50	1,235.67
		3	16.8	107	17	—	2,630	106.72	107/60	1,792.89
		4	7.1	72	8	—	2,035	113.39	72/43	805.07
		5	4.8	60	6	—	2,200	106.72	60/34	512.26
III	Methoxamine	1	5.4	50	6	8.8	1,103	83.38	50/29	450.25
		2	7.0	60	8	13.6	1,018	93.38	60/36	653.66
		3	16.0	83	16	21.5	1,356	80.04	83/51	1,280.64
		4	4.8	49	5	7.8	1,103	80.04	49/29	384.19
III	Hypoxia	1	4.3	47	5	7.1	1,271	100.05	47/29	430.22
		2	4.3	43	5	8.8	847	80.04	43/27	344.17
		3	4.8	30	6	7.1	1,010	50.02	30/20	240.10
IV	Methoxamine	1	9.9	110	6.1	20.1	1,850	68.52	110/85	678.35
		2	17.2	164	15.3	34.9	2,600	70.23	160/116	1,207.96
		3	20.6	178	16.9	37.9	2,800	55.96	163/134	1,152.78
		4	21.0	199	16.5	41.4	3,000	55.96	191/141	1,177.16
		5	19.0	171	17.7	36.0	2,500	50.82	166/127	965.58
		6	17.9	161	15.3	34.4	2,200	55.96	156/120	1,001.68
		7	13.9	137	8.9	28.1	1,700	61.10	133/102	849.29
IV	Control	1	6.5	94	6.86	15.6	3,275	132.47	93/66	861.05
		2	7.1	90	7.27	13.9	3,275	117.06	88/68	831.13
		3	19.7	130	21.8	21.3	3,060	86.22	133/98	1,698.23
		4	20.3	115	30.2	20.3	3,590	45.68	112/74	927.30
		5	16.0	102	17.0	16.8	3,900	50.82	98/55	813.12
		6	15.1	91	12.5	15.1	2,950	48.54	88/44	732.95
		7	11.1	72	8.07	10.5	1,900	48.54	—	538.79

TABLE I—(CONT'D)

DOG NUMBER	EXPERIMENTAL CONDITIONS		LEFT VENTRICULAR END-DIASTOLIC STRETCH INDEX	VENTRICULAR PRESSURE (MM. Hg)		VENTRICULAR PRESSURE AREA (MM. Hg × SEC.) (SYSTOLIC)	MAXIMUM SLOPE OF ISOMETRIC CONTRACTION (MM. Hg/SEC.)	CONTRACTILITY INDEX–STRAIN-GAUGE ARCH (PER CENT OF CONTROL)	AORTIC PRESSURE (MM. Hg) S/D	MAXIMUM CONTRACTILE TENSION INDEX (STRETCH × CONTRACTILITY)
				SYSTOLIC	END-DIASTOLIC					
IV	Epinephrine	1	9.6	126	9.7	18.7	4,220	132.47	126/91	1,271.71
		2	9.6	130	4.03	17.0	5,070	127.33	130/94	1,222.37
		3	14.5	152	11.3	23.2	5,280	122.19	152/122	1,771.76
		4	19.4	177	18.54	25.2	5,805	122.19	177/116	2,370.48
		5	19.2	168	22.85	26.4	6,610	110.20	168/118	2,115.84
		6	16.3	141	14.1	21.6	5,700	142.18	141/110	2,317.53
		7	17.2	158	9.68	15.5	6,020	126.76	158/115	2,180.27
V	Control	1	9.0	160	9	20.6	3,060	110.43	160/121	993.87
		2	13.0	171	13	28.4	3,870	89.01	171/137	1,157.13
		3	14.5	179	13	31.6	3,870	92.34	179/147	1,338.93
		4	27.0	216	30	42.4	4,480	61.40	216/163	1,657.80
		5	12.5	152	12	24.7	3,360	98.53	152/119	1,231.62
		6	9.5	142	10	21.6	3,360	104.24	142/116	990.28
		7	9.3	137	9	20.6	3,360	110.43	137/112	1,027.00
		8	8.4	117	8	17.2	3,060	122.81	117/94	1,031.60
V	Epinephrine	1	6.4	100	6	15.0	2,037	116.14	100/79	743.30
		2	8.2	108	6	16.9	1,630	98.53	108/91	807.95
		3	9.0	130	9	21.3	1,834	86.16	130/111	775.44
		4	9.8	145	10	25.2	2,140	79.97	145/124	783.70
		5	13.0	174	13	32.9	3,055	73.78	174/45	959.14
		6	9.0	120	9	21.2	2,037	82.82	120/102	745.38
		7	8.8	111	8	19.0	2,037	86.16	111/90	758.21
		8	8.4	106	8	17.1	2,140	98.53	106/82	827.65
V	Methoxamine	1	9.6	119	8	19.5	2,440	92.34	117/95	886.46
		2	12.2	150	12	28.5	2,240	55.22	150/130	673.68
		3	13.0	147	13	29.6	2,037	49.03	147/129	637.39
		4	16.0	192	16	38.4	2,440	36.65	192/165	586.40
		5	16.8	214	16	45.7	2,645	30.94	214/178	519.79
		6	11.2	125	10	24.6	1,830	55.22	125/111	618.46
		7	10.6	138	9	25.4	1,935	61.40	138/124	650.84

In several of the dogs, asphyxiation was induced by clamping the respirator tube at the conclusion of the experiment and making a recording at half-minute intervals for 4 to 5 minutes. The animals were all sacrificed at the conclusion of the experiments, and the position of the gauges and cannulae confirmed by postmortem examination.

RESULTS

The results are presented in Table I and include measurements at each condition of: end-diastolic pressure, end-diastolic stretch, systolic pressure of the ventricle, planimetered ventricular pressure area (systolic), the maximal rate of pressure rise (M.R.P.R.), myocardial contractility index (from the strain-gauge arch), the aortic systolic and diastolic pressure, and the product of the contractility index and the circumference which is labeled maximum contractile tension index.

Fig. 1 shows the records obtained in a typical experiment, although only three of the atrial reservoir levels in each phase are indicated instead of the greater number that were actually employed. The maximum rate of rise of the ventricular pressure (M.R.P.R.) measured as the amplitude of the derivative of pressure can be seen to increase in rough proportion to the end-diastolic stretch (circumference) during each of the three illustrated conditions, although showing a disproportionately less steep slope during the effect of methoxamine, and a disproportionately steeper slope during the effect of epinephrine. These disproportionate responses may be seen to be reflected in the changes in myocardial contractility as measured by the excursions of the records of the strain-gauge arch. In the methoxamine experiment the contractility is decreased, whereas in the epinephrine experiment the contractility is increased. These effects of the two drugs were characteristic of all experiments.

The statistical relationship of the M.R.P.R. to the various measured parameters was systematically investigated.

The relationship between the maximum rate of pressure rise (M.R.P.R.) and the peak ventricular pressure, and between M.R.P.R. and the area of the ventricular pressure curve during systole for all measurements in all dogs is shown in Fig. 2. Although there is a highly significant relationship between M.R.P.R. and peak systolic pressure ($r = .624$; $p < .001$) and a significant one between M.R.P.R. and ventricular pressure area ($r = .287$; $.01 > p > .001$), it is apparent that a family of curves is actually plotted for each relationship. A different regression equation is required to accurately describe the relationship between the variables under each of the experimental conditions. Thus, the slope of the isometric contraction per unit pressure peak and per unit pressure area is steeper with epinephrine and less steep with methoxamine than during the control period. Some overlapping of the epinephrine and control conditions resulted from the fact that in some experiments the dosage of epinephrine was inadequate to produce any measurable effect on any of the parameters.

Relationship of M.R.P.R. to End-Diastolic Stretch and Pressures.—A very similar relationship was found when the M.R.P.R. was plotted against end-diastolic pressure and against the end-diastolic stretch (Fig. 3). Again a highly significant relationship was apparent, being very slightly better for the stretch

($r = .484$; $p < .001$) than for pressure ($r = .468$; $p < .001$). The formation of "families of curves" reflecting the different experimental conditions is apparent. The administration of epinephrine resulted in a much steeper slope per unit end-diastolic pressure or stretch than did the administration of methoxamine.

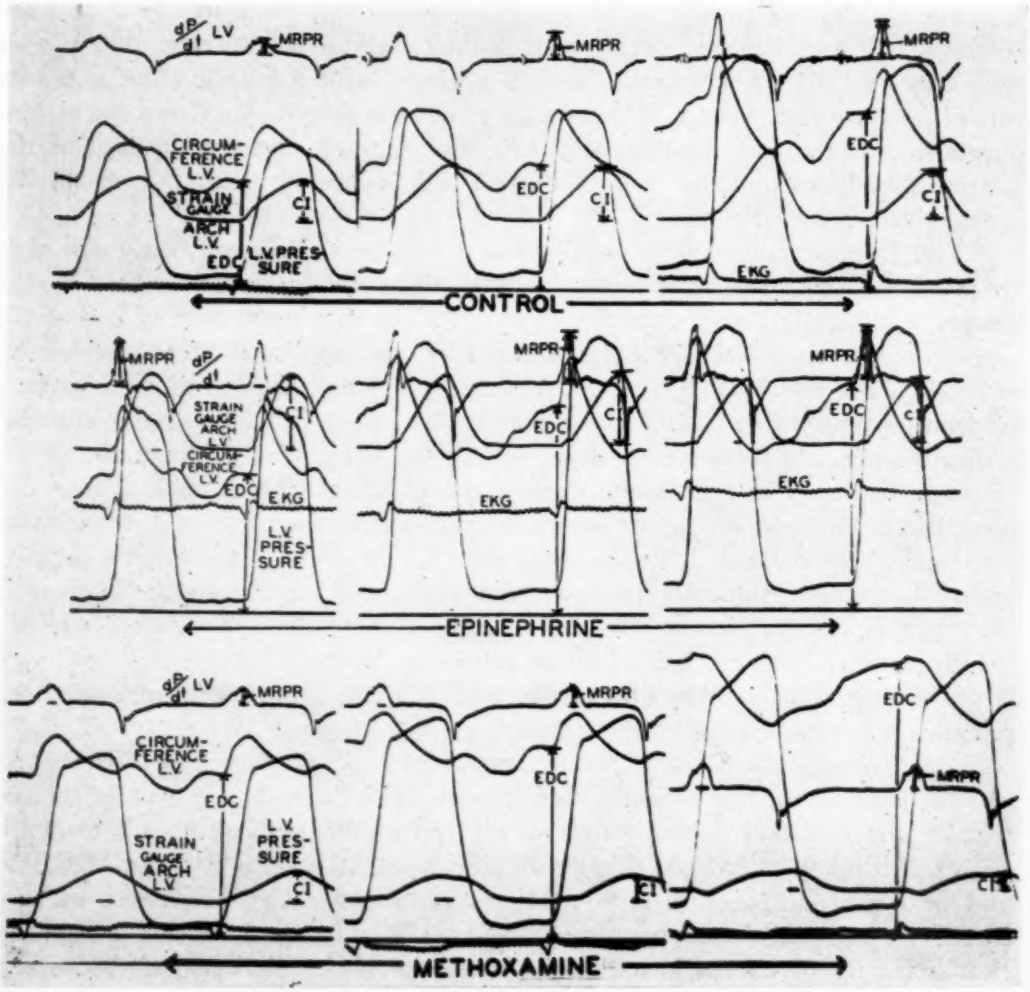

Fig. 1.—The top sequence (labeled *control*) illustrates the changes that were recorded when an atrial reservoir of blood was successively raised so as to induce stepwise changes in ventricular filling without the addition of drugs other than the anesthetics. The middle series reveals the sequential changes observed when similar changes in filling were obtained when the animal was receiving a slight but constant effect from epinephrine. The lowest sequence was obtained by similar maneuvers when systemic resistance was elevated by the administration of methoxamine. The maximal slope of the ventricular pressure pulse (M.R.P.R.) can be equated to the amplitude of the time derivative of the ventricular pressure. The relative state of myocardial contractility can be equated to the total excursion of the strain-gauge arch. An increased M.R.P.R. is apparent when the end-diastolic stretch is increased, and disproportionately so during the infusion of epinephrine. Contrariwise, the slope is disproportionately small, relative to end-diastolic stretch (and end-diastolic pressure) during the infusion of methoxamine. These changes are paralleled by the changes in the excursion of the strain-gauge arch. Of additional interest is the apparent decrease in contractility in the control record at the highest level of ventricular filling.

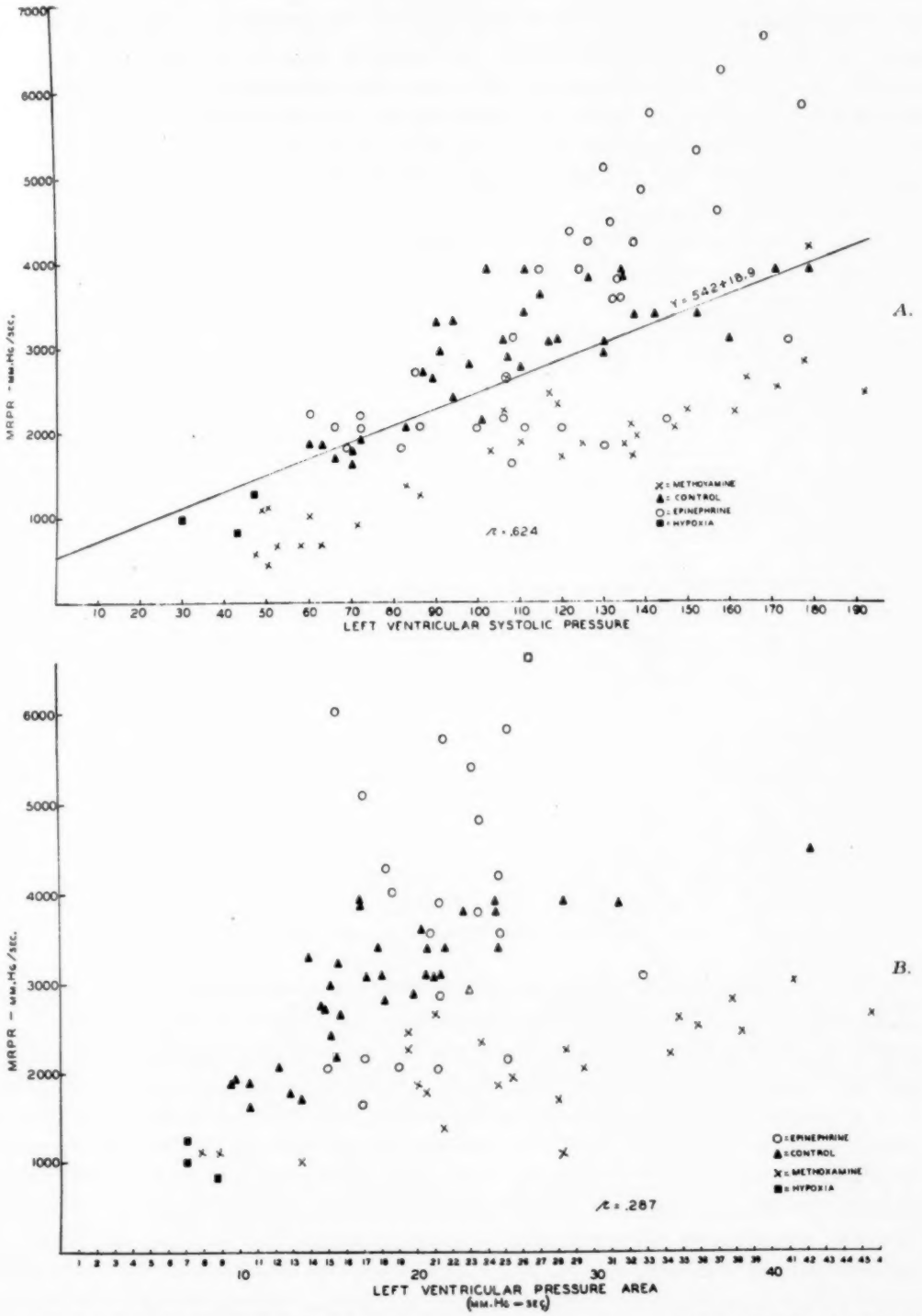

Fig. 2.—*A*, The maximum rate of rise in pressure in the left ventricle, M.R.P.R., is plotted against the peak systolic pressure. Epinephrine increased and methoxamine diminished the rate of rise in pressure for a given level of pressure. These effects are clearly shown by the position of the points in relation to the regression line. *B*, The opposite effects of epinephrine and of methoxamine are seen to be even more striking when the maximum rate of rise in pressure is plotted against the total left ventricular pressure area.

Relationship of M.R.P.R. to Myocardial Contractility.—The correlation between M.R.P.R. and myocardial contractility was quite good ($r = .461$; $p < .001$) (Fig. 4). Unlike the relationship already described, no readily apparent separation into distinct groups according to the conditions of the experiment is seen in Fig. 4. This, possibly, is because there is no indication on the graph as to the end-diastolic stretch of the ventricle at the time of measurement.

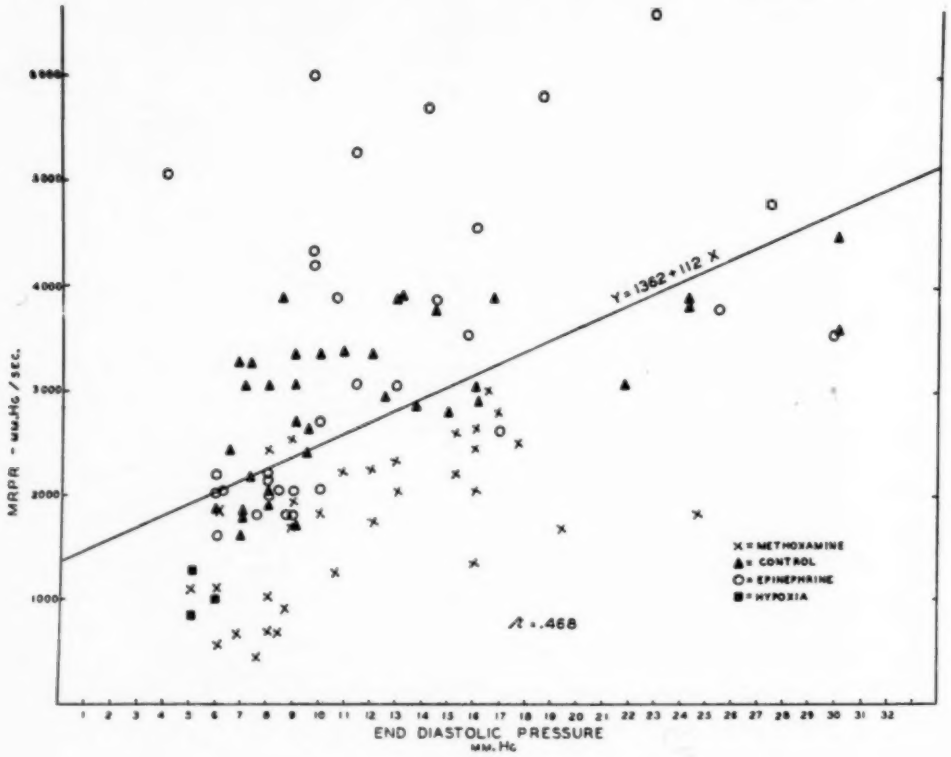

Fig. 3.—*A.* (*For legend see opposite page.*)

The Relationship of M.R.P.R. to the Product of End-Diastolic Stretch and Contractility.—The possibility that the rate of myocardial contraction could be related to a quantitative expression of the net effect of the existing fiber stretch and the existing physiologic condition of the muscle was considered a priori. It is strongly suggested experimentally by the tendency for definite families of curves to be formed when M.R.P.R. was plotted against the end-diastolic stretch as already illustrated. However, it was somewhat surprising to find the extremely good linear relationship between M.R.P.R. and the simple product of the end-diastolic stretch and the contractility index seen in Fig. 5. The coefficient of correlation was very high ($r = .79$; $p < .001$), and there is no apparent separation of the various experimental conditions from the general regression line. Obviously, since M.R.P.R. is directly proportional to the product of the contractility and the stretch, the ratio $\frac{\text{M.R.P.R.}}{\text{E.D.S.}}$ will bear a linear relationship to contractility. This is implicit in the data already presented.

Of practical value would be the ability to measure the myocardial contractility from the ventricular pressure pulse alone, without a strain-gauge arch and without measuring the circumference or volume. That this may be possible with considerable accuracy is shown by Fig. 6, which relates the ratio (M.R.P.R./end-diastolic pressure) to the contractility index as measured by the strain-gauge arch. An excellent correlation was found ($r = .600$; $p < .001$).

When the conditions of the experiment, the complex calibrations employed, and the random error involved are considered, this correlation is most encouraging.

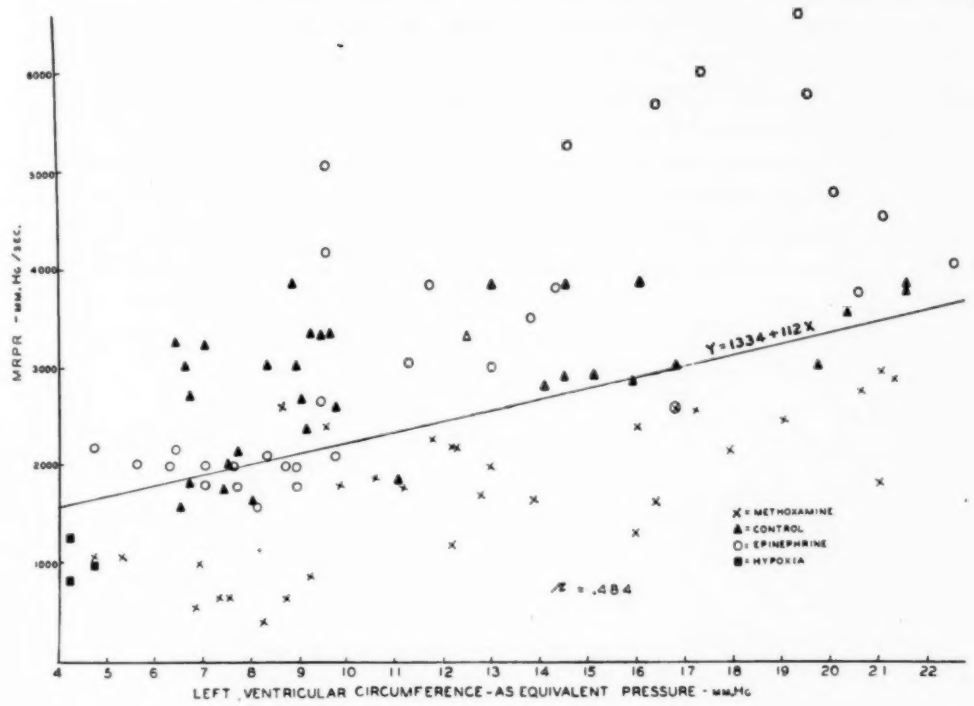

Fig. 3.—*B*.

Fig. 3.—*A*, The control observation indicates a faster rate of rise in pressure in the left ventricle, M.R.P.R., at higher levels of end-diastolic pressure. Epinephrine increased and methoxamine diminished the rate of rise in pressure for a given initial pressure. *B*, The left ventricular end-diastolic stretch index (determined from the pressure-circumference relationship) is plotted against M.R.P.R. For a given initial stretch, epinephrine increased and methoxamine diminished the rate of rise in pressure. It should be noted that the distribution of points in Fig. 2 as well as in Fig. 3 results in "families" of curves with respective elevation and depression by epinephrine and methoxamine.

DISCUSSION

Otto Frank,[1] in 1895, from his experiments on the isometric contraction of the isolated heart of the frog, concluded that the rate of rise in pressure, like the tension produced by the contraction, was determined by the tension upon the ventricle at the end of diastole. This conclusion was supported by the observations of Wiggers[2] in regard to the mammalian heart. The present study demonstrates a highly significant relationship between the rate of rise in pressure and the end-diastolic stretch and end-diastolic pressure even when all observations from all dogs were taken as homogeneous data. However, of considerable added

interest was the finding that the maximal rate of rise in pressure (M.R.P.R.) relative to end-diastolic stretch was systematically increased by the administration of epinephrine and systematically decreased by the administration of methoxamine. The resulting "family of curves" is shown in Fig. 3,*B*. Since epinephrine resulted in an increased myocardial contractility, as measured by the strain-gauge arch, and methoxamine had the opposite effect, it was not surprising to find that this formation of a family of curves was reflected by a significant relationship between M.R.P.R. and the "contractility index" obtained by the strain-gauge arch, as shown in Fig. 4.

The most meaningful and interesting relationship obtained, however, was that between M.R.P.R. and the *product* of the contractility index and the stretch index. The linearity of this relationship is most striking. Upon consideration of the initial assumption of an identical myocardial contractility for all dogs at a given filling pressure, which, if not true, would in itself introduce considerable scatter of the points in addition to inevitable errors in measurements, the high degree of correlation found is impressive. An additional cause for the observed scatter not due to chance is the Laplace effect, discussed hereinafter.

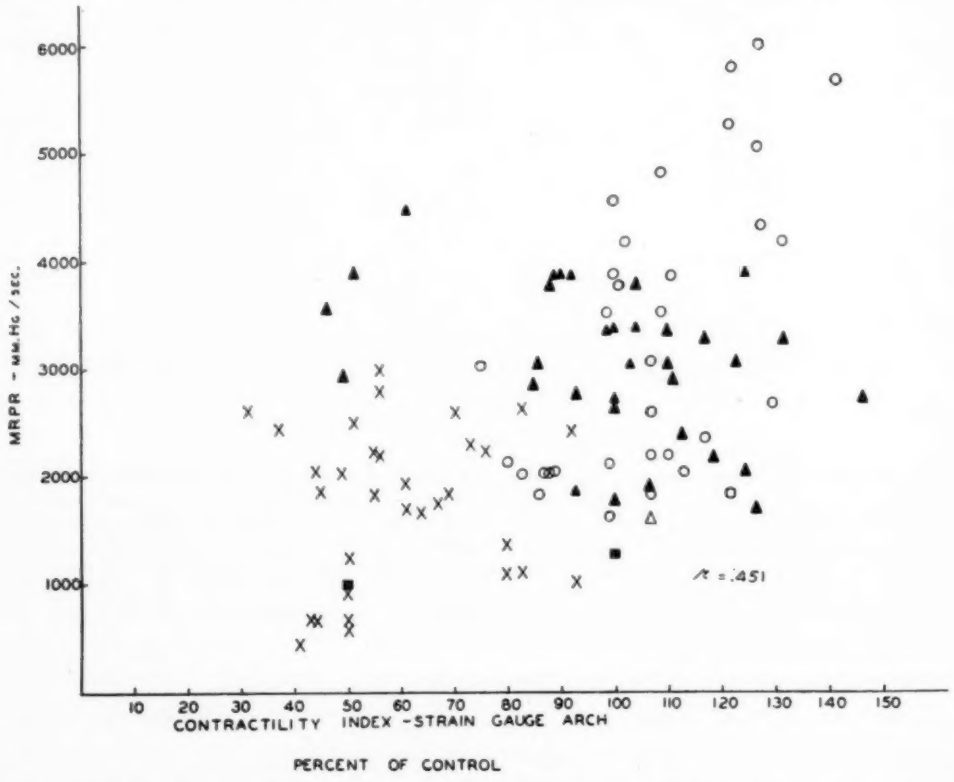

Fig. 4.—The data for the left ventricular contractility index were obtained from the strain-gauge arch. Since the length of muscle involved was constant in a given animal, the deflections were a direct index of change in tension in a single myocardial strip in that animal. The unit of the X axis is the percentage of the tension developed by the strain-gauge arch at a standard end-diastolic pressure during the "control" condition. A significant relation between the rate of rise in pressure (M.R.P.R.) and the contractility index is shown. The values for both measurements tended to be lower after methoxamine and higher after epinephrine than during the control period. There is no tendency to form a "family" of curves according to the indicated conditions of the experiment.

In view of these considerations, it appears reasonable to conclude that the rate of rise in pressure in the ventricle during isometric systole is a linear function of the product of the end-diastolic stretch and the contractility of the ventricle.

Although this observation per se is of considerable interest, additional insight into its meaning can be obtained by examining the product of stretch and contractility more closely. Stretch, as defined previously, is a measure of the degree of displacement of the ventricular muscle fibers from their resting (unstretched) length. Contractility has been defined for this experiment as the maximum tension generated during contraction per unit stretch. This quotient was measured by the strain-gauge arch. Since the units of contractility thus measured are tension per unit diastolic stretch, and the diastolic stretch of the whole ventricle has been measured, it follows that the units of the product of these parameters are maximum tension of the whole ventricle (for an isometric contraction). Maximum tension/stretch × stretch = maximum tension. It is understood that the units are relative, not absolute, that the segment of myocardium under the strain gauge is assumed to be representative of the entire ventricle, and that interpretation of results must allow for the Laplace effect. It is important and intriguing to note that this product of contractility and stretch is not an index to the actual tension produced per beat by the ventricle, but is in effect a *prediction* of the

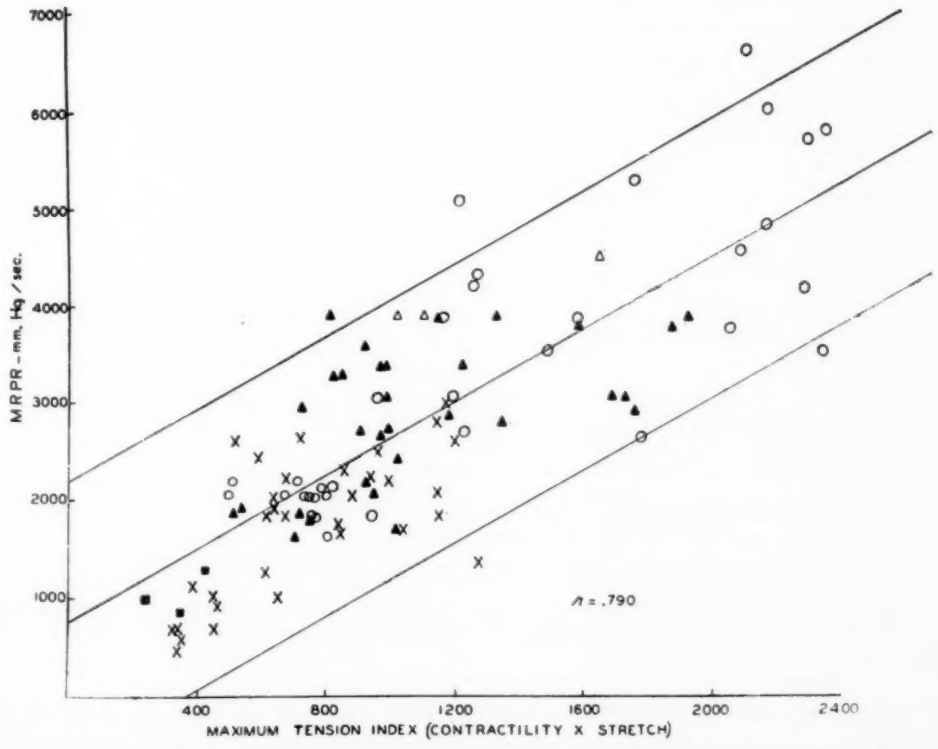

Fig. 5.—When the maximum rate of rise in pressure (M.R.P.R.) is plotted against the *product* of the contractility index and the stretch index, a highly significant linear relationship is found. The lines parallel to the regression lines indicate 2 standard deviations. No apparent systematic deviation from the general regression line, according to the experimental conditions, is seen. This observation suggests that the M.R.P.R. of the ventricle is directly proportional to the maximum tension that would be generated during a *completely* isometric contraction of the ventricle.

maximum tension that would have been produced if shortening of the fibers (during ejection) had not occurred. This follows from the fact that the tension measured by the strain-gauge arch is that of an isometric contraction of the sampled segment. *Thus we find that the maximum rate of rise in pressure during the contraction phase of a ventricular systole, during which shortening occurs, is proportional to the maximum tension that would have been attained had ejection shortening not been allowed.* This conclusion is supported by an earlier observation of Wiggers.[2] He found that the rate of rise in pressure in the ventricle during isometric contraction was not altered in the first beats following abrupt ligation of the aorta although the ventricular pressure rose to a higher level. Only after increased diastolic stretch resulted did a measurable increase in the slope of the ventricular pressure pulse occur.

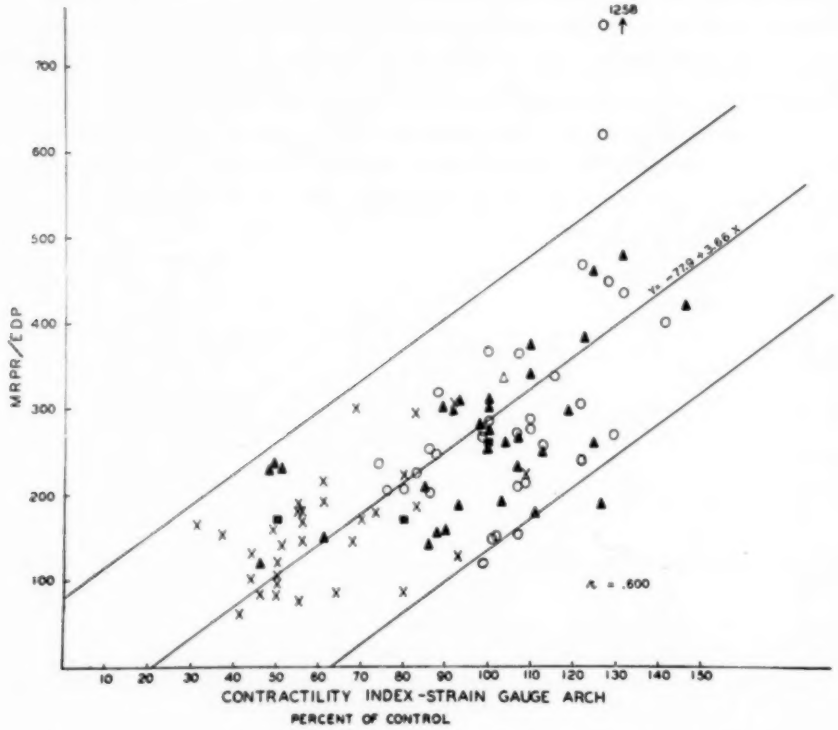

Fig. 6.—The contractility index derived from the strain-gauge arch is actually a measure of the maximum tension generated during an isometric contraction of a fixed segment of muscle under a constant stretch. As seen in Fig. 5, M.R.P.R. is proportional to the maximal tension that would be produced by the entire ventricle. It follows then that the quotient M.R.P.R./stretch would be a measure of the same aspect of myocardial function measured by the strain-gauge arch. In this figure, end-diastolic pressure was used as an index to stretch. The observed correlation between these variables is highly significant ($p < .001$).

As mentioned above, any consideration of the rate of rise in pressure must include a consideration of the Laplace relationship between pressure and tension.[9] The rate of change in pressure is a reflection of the rate of change in tension, modified by the size and shape of the ventricle. If the ventricle is assumed to be a cylinder, then $P = T/R$, where P = pressure inside the cylinder, T = tension in the curved wall of the cylinder, and R = radius of the cylinder.

Since all of the variables are functions of time in the ventricle, this equation is differentiated with respect to time:

$$dp/dt = \frac{R^{dT}/dt - T\ dr/dt}{R^2}$$

where dp/dt = rate of change of pressure with respect to time, dT/dt = rate of change of tension with respect to time, and dr/dt = rate of change of radius with respect to time. Since during isometric systole, dr/dt is zero, the equation simplifies for isometric systole to dp/dt = dT/dt/R. This relationship demonstrates a systematic cause of the scatter seen in Fig. 6, which relates M.R.P.R. to the product of stretch and contractility. The high degree of correlation, in view of this factor, becomes even more impressive and lends considerable weight to the probability that the rate of contraction of the ventricular myocardium is a linear function of the *product* of the end-diastolic stretch of the ventricle and its contractility. It would also follow that the rate of contraction and the rate of increase in tension would be directly proportional to the maximum tension produced by an isometric contraction of the ventricle. Further direct experimentation is needed in order to determine the accuracy of these conclusions.

There are a number of readily visualized potential applications for the information obtained from this study. One of these is the possibility that a useful index to myocardial contractility in the intact man or animal can be obtained from the ventricular pressure pulse alone. This possibility is illustrated in Fig. 6, which relates the quotient M.R.P.R./end-diastolic pressure to the contractility index derived from the strain-gauge arch. The highly significant correlation (r = .600) between these two estimates of contractility is implicit in the linear relationship of M.R.P.R. to the product of contractility and diastolic stretch shown in Fig. 5, if diastolic pressure can be equated to diastolic stretch. The Y intercept of that figure is close to the origin, relative to the average magnitude of the Y values actually obtained. This means that the relation between M.R.P.R. and the product of diastolic stretch and contractility may be closely approximated by the following equation: M.R.P.R. = K × contractility × diastolic stretch, where K is a constant of proportionality.

Now, if both sides of the equation be divided by "diastolic stretch," the following equation results: M.R.P.R./Diastolic stretch = K × contractility. If one used end-diastolic pressure in place of diastolic stretch (because its measure is more readily obtainable), there results: M.R.P.R./end-diastolic pressure = K × contractility.

The demonstrated correlation is not perfect. However, it is to be remembered that the initial calibration of the strain-gauge arch was based upon the doubtful assumption that the contractility in the control period was the same in all dogs. Moreover, the measured contractility in any given dog affected might have been affected to an unmeasurable extent by participation of the myocardial syncytium adjacent to the strain-gauge arch. Since these adjacent fibers were not of constant length, the force of their contraction was not a direct reflection of myocardial contractility. This application is explored more fully in another communication.[10]

Since the duration of the phase of isometric contraction of the cardiac cycle is in part a function of the rate of rise in pressure, it is apparent that the principles

discussed here would be of importance when the physiologic determinants of the duration of this phase of the cardiac cycle are considered.

SUMMARY

The phasic pressure, time derivative of pressure, circumference and isometric contractile tension (Walton-Brodie strain-gauge arch) of the left ventricle have been simultaneously recorded in a series of anesthetized, thoracotomized, innervated dogs. These parameters were recorded at multiple levels of filling pressure induced by variations in the height of a large reservoir of blood connected to the left atrium. Variations in myocardial function and systemic resistance were induced by the administration of epinephrine and methoxamine. The atrial reservoir was systematically lowered and raised during each experimental condition in order to induce variations in ventricular filling. In all, 108 experimental situations were recorded in 5 consecutive animals.

The maximal slope of the isometric contraction phase of the ventricular pressure pulse (M.R.P.R.) ranged from 456 to 6,610 mm. Hg per second. It was shown that when all observations were considered, M.R.P.R. had a significant correlation with peak ventricular pressure ($r = .624$), ventricular pressure area ($r = .287$), ventricular end-diastolic stretch ($r = .484$), and ventricular end-diastolic pressure ($r = .468$). All of these relationships showed a strong tendency to form distinct families of curves with M.R.P.R. per unit systolic pressure, stretch, or end-diastolic pressure, being greater while epinephrine was being administered than in the control period. Conversely, M.R.P.R. was less per unit systolic pressure, circumference, or end-diastolic pressure when methoxamine was administered. Since epinephrine produced an increased myocardial contractility (isometric systolic tension per unit stretch), and methoxamine, presumably through vagal influences, produced a decreased myocardial contractility, it was not surprising that a highly significant correlation between M.R.P.R. and contractility was found ($r = .451$). A very good linear relationship was found between M.R.P.R. and the *product* of contractility (strain-gauge arch) and the end-diastolic stretch of the ventricle ($r = .790$). This product was considered as an index to the potential isometric contractile tension of the entire ventricle. It was, therefore, suggested that M.R.P.R. is directly proportional to the maximum tension potential of the ventricle at the onset of contraction.

Possible applications of these findings were briefly discussed.

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REFERENCES

1. Frank, O.: Zur Dynamik des Herzmuskels, Ztschr. f. Biol. **32**:370, 1895.
2. Wiggers, C. J.: Some Factors Controlling the Shape of the Pressure Curve in the Right Ventricle, Am. J. Physiol. **33**:382, 1914.
3. Patterson, S. W., Piper, H., and Starling, E. H.: The Regulation of the Heart Beat, J. Physiol. **48**:465, 1914.
4. Rushmer, R. F.: Work of the Heart, Mod. Concepts Cardiovas. Dis. **37**:473, 1958.

5. Starling, E. H., and Visscher, M. B.: The Regulation of the Energy Output of the Heart, J. Physiol. **62**:243, 1927.
6. Rushmer, R. F.: Length Circumference Relations of the Left Ventricle, Circulation Res. **3**:639, 1955.
7. Boniface, K. J., Brodie, O. J., and Walton, R. P.: Resistance Strain Gauge Arches for Direct Measurement of Heart Contractile Force in Animals, Proc. Soc. Exper. Biol. & Med. **84**:263, 1953.
8. Goldberg, L. I., Cotten, M. V., Darby, T. D., and Howell, E. V.: Comparative Heart Contractile Force Effects of Equipressor Doses of Several Sympathomimetic Amines, J. Pharm. & Exper. Therap. **108**:177, 1953.
9. Burton, A. C.: The Importance of the Shape and Size of the Heart, AM. HEART J. **54**:801, 1957.
10. Carroll, J. F., Hefner, L. L., Jones, W. B., Prieto, G., Coghlan, H. C., and Reeves, T. J.: A Comparison of Methods for Measurement of Myocardial Contractility. (To be published.)

The Use of Biplane Angiocardiography for the Measurement of Left Ventricular Volume in Man

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Application of volumetric techniques for the study of cardiovascular physiology and pathophysiology in man is dependent on the development of a satisfactory method for quantifying specific cardiac chamber volumes. Robb and Steinberg,[1] and later Lind and Wegelius,[2] suggested the use of angiocardiography as a means of determining chamber volumes. Soloff and associates[3] have described semiquantitative measurements of left atrial volumes by means of angiocardiography and biplane filming. Preliminary studies concerned with quantifying left ventricular volume from biplane angiocardiograms have been previously reported.[4] Chapman and associates[5] more recently adapted biplane angiocineroentgenography for quantitative study of left ventricular volumes in man.

The calculation of ventricular volume from biplane angiocardiographic films presents three major problems: (1) image distortion from nonparallel x-ray beams due to the proximity of the x-ray tubes; (2) varying left ventricular image projections on the x-ray films resulting from differing left ventricular spatial positions; and (3) selection of a suitable geometric reference figure for the purpose of volume calculation.

These studies were undertaken to develop and evaluate methods for solving each of these problems, and thereby to make it possible to quantify left ventricular chamber volumes from biplane angiocardiograms in man.

METHODS

Eighty-four observations were made on 9 postmortem hearts at volumes which varied from 25 to 350 c.c. The left ventricles of these hearts were filled with varying known amounts of barium sulfate paste, selected because leakage was a major problem when aqueous contrast materials were used. Each postmortem heart was prepared for study by washing the left ventricular cavity free of clots, suturing the free edges of the mitral valve together, and ligating the coronary arteries at the base of the aorta. A plastic catheter was inserted into the left ventricular cavity from the base of the aorta, and the aorta was clamped just above the aortic valves. The preparation was

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then suspended over the angiocardiographic unit so that the relationships of the left ventricle with respect to position, film, and x-ray tube distances approximated those found during angiocardiography in man. Of the 84 individual observations, 30 were performed on 2 hearts placed in differing positions and rotations with respect to the x-ray tubes and films. Simultaneous biplane films were taken with each 25-c.c. injection of contrast material through the catheter. Individual heart observations were terminated by either heart rupture or leakage of contrast material.

In addition, the effects of rotation on the projections of the left ventricle were studied by the use of two ellipsoid-shaped clay models, made radiopaque by barium sulfate paste kneaded into the clay. The long axis of each figure was defined by a steel wire. These clay models were placed in differing positions and rotations with respect to the x-ray films and tubes.

X-ray films, 14 by 14 inches, were recorded by a Schonander biplane angiocardiographic unit. The center of each cassette face was arranged to coincide with the line of the central beam of its respective x-ray tube. These spots (the center of each cassette face) were marked by small lead markers, and recorded as a radiopacity on each film. These markings on the x-ray films were used in correcting for the distortion of the heart shadow resulting from the proximity of the x-ray tubes and accordingly nonparallel x-rays.

Correction for Nonparallel X-Ray Beams.—It has been previously demonstrated, and is well known, that for tube-to-film distances of less than 6 feet, there is x-ray image distortion, which is determined by the tube-to-film and object-to-film distances. Lysholm and Jonsell, and later Kjellberg, were the first to correct for x-ray distortion in calculating total heart volume from biplane films.[6-8] They pointed out that the distortion of an object on each film can be expressed as illustrated in Fig. 1,

$$a_t = \frac{(h-p)\ a_p}{h} \tag{1}$$

where a_t = true length of an object; a_p = projected length; h = tube-to-film distance; p = object-to-film distance. Therefore, to correct for x-ray distortion, both the tube-to-film and object-to-film distances for each film must be known.

By the use of biplane films, taken at right angles, it is possible to calculate the distance of an object from both the anteroposterior (A-P) and lateral x-ray films. This can be done by determining the relationship of the object to two planes: one containing the central beam of the lateral x-ray tube and parallel to the A-P x-ray film, the other containing the central beam of the A-P x-ray tube and parallel to the lateral x-ray film. Each plane defines a line on its respective x-ray film. This line is parallel to the opposite x-ray film and passes through the lead marker which is photographed on each film. This is illustrated by planes A and B of Fig. 3. These planes which contain the central beams are used as references, for they define distances that have a known amount of x-ray distortion. This is because the distance of the central beam of each x-ray tube to the opposite film and the x-ray tube-to-film distances are fixed and can be measured directly.

Fig. 2 represents an object at point P with its distorted projections on the A-P and lateral films. p_1 represents the distance from the lateral film to the plane containing the A-P central beam (plane B, Fig. 3); p_a similarly represents the distance from the A-P film to the plane containing the lateral central beam (plane A, Fig. 3). a_t, 1_t represent the undistorted distance of P from these planes.

This is the same as the perpendicular distance of an undistorted projection of P to the previously described line passing through the lead marker on each respective A-P and lateral film. a_m, 1_m represent the distorted or observed perpendicular distances of a_t and 1_t on each film. h_a, h_1 are the respective film-to-tube distances.

From Fig. 2, by utilization of the relationships of similar triangles (shaded triangle to respective large triangle), the following proportions exist:

$$\text{for the A-P plane } \frac{a_m - a_t}{1_t + p_a} = \frac{a_m}{h_a} \tag{2}$$

$$\text{for the lateral plane } \frac{1_m - 1_t}{a_t + p_1} = \frac{1_m}{h_1} \tag{3}$$

Point P is common to both planes. These equations can be solved simultaneously for a_t and 1_t in terms of a_m and 1_m, since h_a, h_1, p_a, and p_1 are the tube-to-film and central beam-to-film distances and can be measured directly. Thus:

$$a_t = \frac{a_m\,[h_1\,(ha - pa) \pm 1_m\,(h_1 - p_1)]}{h_a\,h_1 \pm a_m\,1_m} \tag{4}$$

$$1_t = \frac{1_m\,[ha\,(h_1 - p_1) \pm am\,(ha - pa)]}{h_a\,h_1 \pm a_m\,1_m} \tag{5}$$

Rather than use Equations 4 and 5, one can construct a grid-graph for individual x-ray equipment and read a_t and 1_t directly, knowing am and 1m.

The plus-minus relationships in Equations 4 and 5 are determined by the position of point P with respect to each x-ray film and the plane parallel to the opposite film and containing the central beam of each x-ray tube (planes A and B of Fig. 3). Positive values apply to positions which lie closer to the opposite film, negative values to positions which lie farther from the opposite film, than planes A and B. The distances of these planes from the respective A-P and lateral films are p_a and p_1. Then the distance of an object at point P from the A-P and lateral films is equal to $p_a \pm 1_t$ and $p_1 \pm a_t$, respectively. Since both a_m and 1_m can be measured from the finished films, the undistorted position of any point on the x-ray film can be determined from Equations 4 and 5. Thus, when the position of the central x-ray beam and the x-ray film and x-ray tube relationships are known, it is possible to determine the object-to-film distance. When the object-to-film distance is known, it is possible to correct for nonparallel x-ray beam distortion by using Equation 1.

Spatial Representation Using Biplanar Images.—Once images have been corrected for x-ray distortion due to proximity of the x-ray tubes, it is possible to calculate the true spatial length and direction of an object from its projections on the two x-ray films. This is accomplished by determining the projections of the image on a spatial coordinate system. A triaxial geometric reference figure is used, as is illustrated in Fig. 3. The origin of the system is defined by the point of intersection of the central beams of the x-ray tubes. The axes are defined by the intersection of three planes: one parallel to the A-P film and containing the

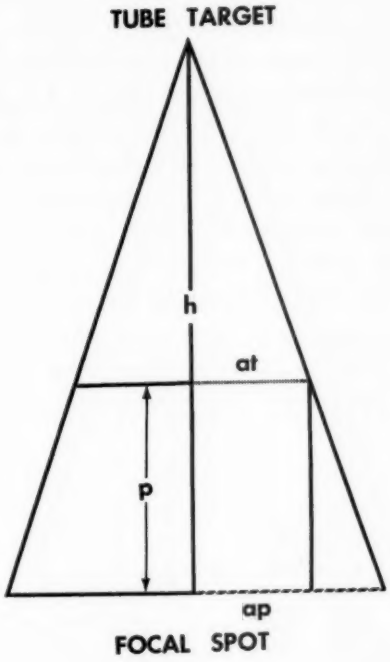
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Fig. 1.

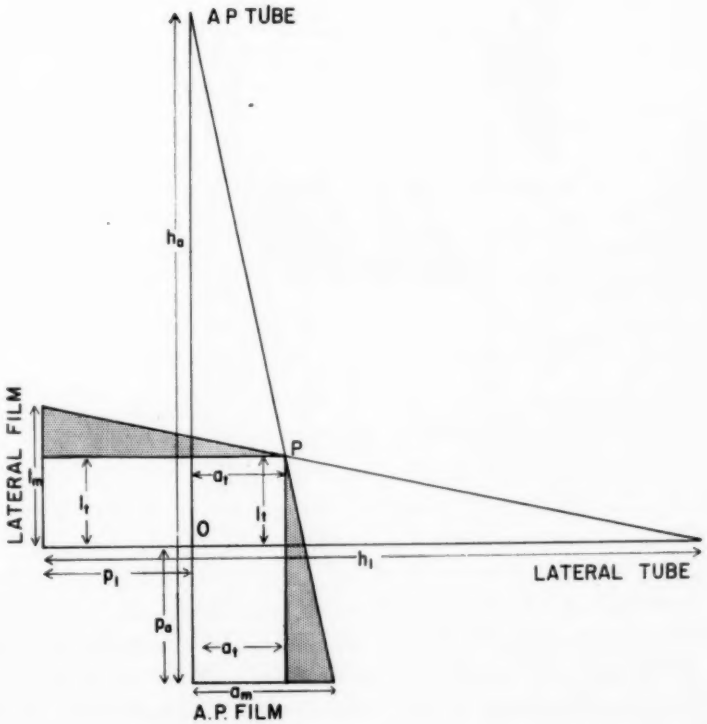
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Fig. 2.

lateral central beam (plane A), one parallel to the lateral film and containing the A-P central beam (plane B), and one containing both central beams and perpendicular to both films (plane C). The coordinate axes can then be defined as follows: X-axis by the intersection of planes A and B, Y-axis by the intersection of planes A and C, and Z-axis by the intersection of planes B and C. This triaxial reference figure has a projection on each of the A-P and lateral films: the X-Y axes and their component projections are contained on the A-P x-ray films, X-Z axes and their component projections are contained on the lateral x-ray films. The X-axis is common to both films and its projection on each x-ray film is used in defining the plus-minus characteristics in Equations 4 and 5 that are used in calculating correction factors. A projection of the coordinate axes can be constructed on each x-ray film: the X-Y axes on the A-P film and the X-Z axes on the lateral film. If the locations of two points that define a line are

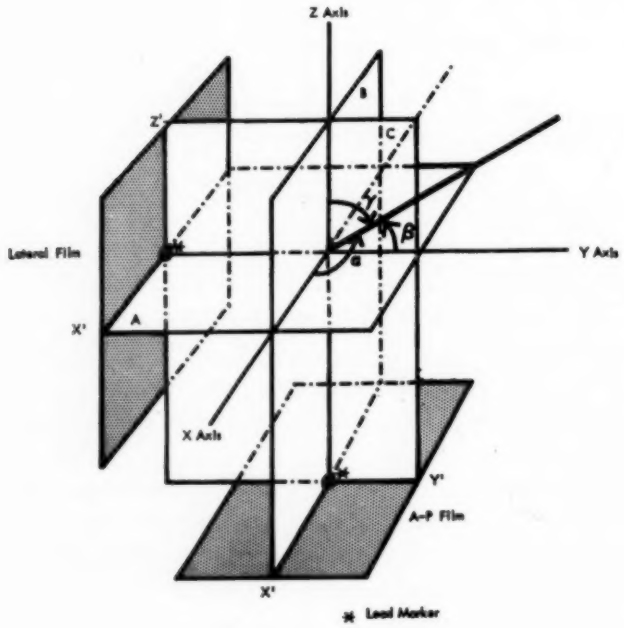

Fig. 3.

corrected for distortion due to nonparallel x-ray beams, the X, Y, and Z components of the line can then be measured directly from the x-ray films. This is illustrated in Fig. 4, which represents the projection of a left ventricle on the A-P and lateral films. To calculate the apex to aortic valve distance, the apex and aortic valves are identified on each film: apex at s and aortic valves at t. The undistorted position of the apex and aortic valves (s′ and t′, respectively) can be calculated by Equations 4, 5, and 1. Then the components (X_c, Y_c, Z_c) of line s′-t′ on each axis can be measured directly. Since the X-axis is common to both films, the X component in both films must be equal and serves as a check on the method. The undistorted or true length (p) of the designated line s′-t′ can be calculated from biplane x-ray films by the following equation:

$$p = \sqrt{(X_c)^2 + (Y_c)^2 + (Z_c)^2} \tag{6}$$

p = spatial length

The direction of the line in space may be defined by its polar angles, α, β, γ:

$$\alpha = \cos^{-1}(X_c/p) \tag{7}$$

$$\beta = \cos^{-1}(Y_c/p) \tag{8}$$

$$\gamma = \cos^{-1}(Z_c/p) \tag{9}$$

These angles are illustrated in Fig. 3. By the application of this method of analysis to the projected biplanar images, both the spatial direction and magnitude of any defined line on the x-ray films can be calculated.

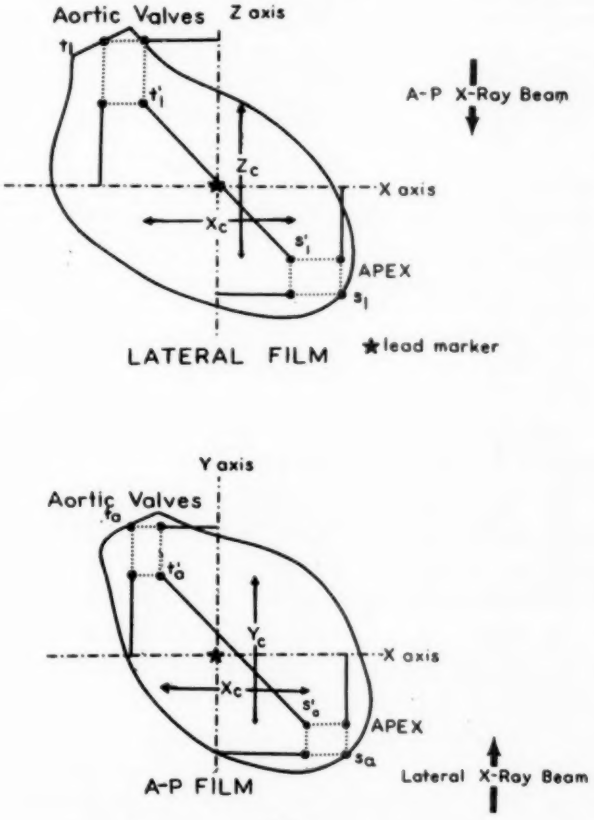

Fig. 4.

These methods for correcting for distortion due to spatial position and nonparallel x-rays were tested. Thirteen biplane x-rays were taken of a thin steel wire of known length with differing positions and rotations. The results are contained in Table I (the long axis, p of the clay model). The known length of the wire was 12.1 cm., as compared with a mean calculated length (p) of 12.2 ± 0.2 cm.

Selection of a Geometric Reference Figure for Calculation of Volume.—Earlier workers[7-9] demonstrated that total heart volume calculated from an ellipsoid reference figure gave results which agreed closely with directly measured heart volumes. An ellipsoid reference figure was also used by Arvidsson[10] in his studies of left atrial and left ventricular volumes. In the present studies, clay models of the left ventricle, patterned from opacified left ventricular chambers, were constructed and closely resembled an ellipsoid, which was the reference figure used in calculating left ventricular chamber volume. The formula for the volume of an ellipsoid is:

$$V = 4/3\ \pi\ abc \qquad (10)$$

where V = volume; a = one half the length of the major axis; and b, c = one half the lengths of the minor axes. To use an ellipsoid reference figure for calculating left ventricular chamber volume, the lengths of these axes must be determined.

TABLE I

	L_e (CM.)	p (CM.)	b (CM.)	c (CM.)	CALCULATED VOLUME (CM.^{3})	
					USING L_e	USING p
Known length	12.1	12.1				
Model No. 2					VOLUME BY DISPLACEMENT (198 CM.^{3})	
1	11.92	12.05	2.76	2.85	196	197
2	11.96	12.21	2.81	2.76	194	198
3	11.52	12.36	2.73	2.77	183	196
4	11.58	12.40	2.73	2.75	182	195
5	10.96	12.48	2.93	2.76	186	211
6	10.66	12.40	2.88	2.78	179	204
Mean			2.81 ± 0.08	2.78 ± 0.04		
Model No. 3					VOLUME BY DISPLACEMENT (190 CM.^{3})	
1	12.26	12.06	2.67	2.76	189	186
2	11.88	12.07	2.74	2.78	190	192
3	10.06	12.10	2.67	2.70	152	182
4	10.74	11.78	2.68	2.73	164	180
5	9.78	12.24	2.71	2.68	148	186
6	12.02	12.05	2.71	2.62	178	179
7	11.96	11.97	2.72	2.67	182	182
Mean	11.3 ± 0.81	12.2 ± 0.20	2.70 ± 0.03	2.71 ± 0.06		

L_e: Longest image length regardless of whether in A-P or lateral film. p: Calculated spatial length. b and c: Calculated transverse diameters (see Equation 11). All values have been corrected for non-parallel x-rays.

Various methods for determining the lengths of these axes for the purposes of calculation of volume have been tested. It should be appreciated that unless a given axis lies parallel to one of the x-ray films, it cannot be measured directly, but what is measured is a projection of that axis on the films. The effects of rotation of the heart on the projection of these axes were tested in two ways: (1) by use of the previously described clay models, and (2) by analysis of data from two postmortem hearts that were rotated to various positions. A total of 13 observations on the clay model were made by biplane filming under conditions of a wide variety of changes in position and rotation, only 2 of which compared to the "usual" orientation of the left ventricle in man. The ends of the wire, which designated the major axis of the parent ellipsoid figure, did not coincide with the margins of the projected image in one, or both, of the simultaneously recorded films in the majority of observations. Thus, what appeared to be the major axis of the ellipsoid on the films did not correspond to the true major axis. This is illustrated in Table I, in which the longest directly measured lengths of the images are corrected for nonparallel x-ray distortion (L_c) and compared with the calculated spatial lengths (p) and known length. With rotation, values for L_c differ from the known length when the long axis is not parallel to one of the x-ray films.

The transverse or minor axes on each film were calculated from the planimetered area and the longest measured length of its respective image. As was shown by Arvidsson,[10] the projection of an ellipsoid is an ellipse. Therefore, the length of a minor axis (d) can be calculated as follows:

$$d = \frac{4A}{\pi 1} \tag{11}$$

where 1 = the length or major axis in a given film, and A = the planimetered area. These calculated transverse diameters, when corrected for nonparallel x-ray distortion, showed little scatter regardless of position or rotation of the figure (b and c of Table I). This analysis was also applied to the 30 observations on human postmortem hearts placed in differing positions and rotations. Calculated transverse diameters for the postmortem hearts differed by not more than 0.15 cm. for various rotations and positions of the heart at the same volume. Kjellberg and Larsson[8] found the same relationship to be true for a model of the entire heart. It is concluded that positional change results in an image with a distorted projection of the major axis, but the calculated transverse diameters are essentially unchanged.

Analysis of Methods for Calculating Left Ventricular Volume.—In the calculation of left ventricular chamber volumes of postmortem hearts, each calculated volume was compared to its respective known volume for each method of calculation.

Method I (spatial method): Since the apex to the mid-aortic valve length is the longest chamber distance in the postmortem heart, it represents the longest axis of the reference ellipsoid figure; therefore, the apex and aortic valves were identified on each film, and the spatial apex to aortic valve distance was determined. The following data were obtained from each set of biplane films: (1) The

image of the left ventricle was traced and the area planimetered. (2) The apex and aortic valves were marked. (3) Transverse diameters were calculated, using Equation 11. (4) The X, Y, and Z component lengths were directly measured from each film after correction for the distortion due to nonparallel x-ray beams, as previously described. (5) The spatial aortic valve to apex length was calculated by Equation 6.

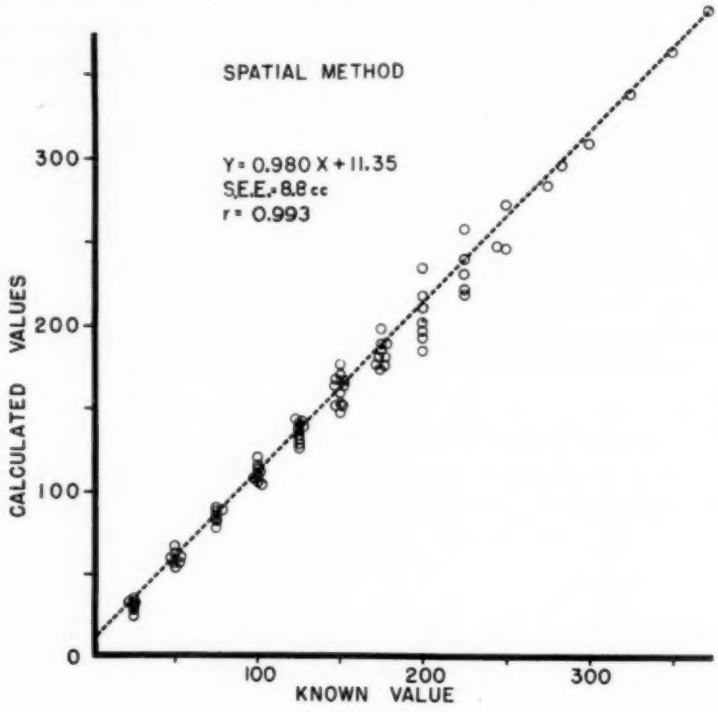

Fig. 5.

This is illustrated in Fig. 4. All transverse diameters were corrected for nonparallel x-rays by the use of a mean correction factor, determined by the perpendicular distance of the estimated center of mass of the image to the constructed X-axis. The volume can then be expressed as:

$$V = 4/3 \cdot \pi \cdot p/2 \cdot d'_a/2 \cdot d'_l/2 \qquad (12)$$

where V = volume of the left ventricular chamber, in cm.^{3}; p = spatial distance of the apex to aortic valves, in cm.; d'_a = corrected diameter in A-P plane, in cm.; and d'_l = corrected diameter in lateral plane, in cm. The regression line and standard error of estimate (S.E.E.) for this method are illustrated in Fig. 5. Volumes of the clay model as calculated by this method are compared with the known volumes in Table I. Known and calculated volumes of this model were related to a regression line with a S.E.E. of 5.1 c.c.

Method II (longest measured length): The longest measured image length in each film was corrected for distortion due to nonparallel x-rays by the same mean correction factor used in calculating the transverse diameters in Method I. The

longest corrected length was used regardless of whether it occurred in the A-P or lateral films, since it was assumed that despite positional changes, a length approaching the length of the major axis would be projected on one of the films. The transverse diameters for each plane were derived as in Method I. The chamber volume was expressed by the relation,

$$V = 4/3 \cdot \pi \cdot 1'/2 \cdot d'_a/2 \cdot d'_l/2 \qquad (13)$$

where V = volume of left ventricular chamber, in cm.^{3}; d'_a, d'_l are the corrected diameters, in cm., as previously described in the spatial method; and $1'$ = the longest corrected length in either film, in cm. Results for this method are illustrated in Fig. 6, and for the clay model in Table I. Known and calculated volumes for the clay model were related with a S.E.E. of 10.7 c.c.

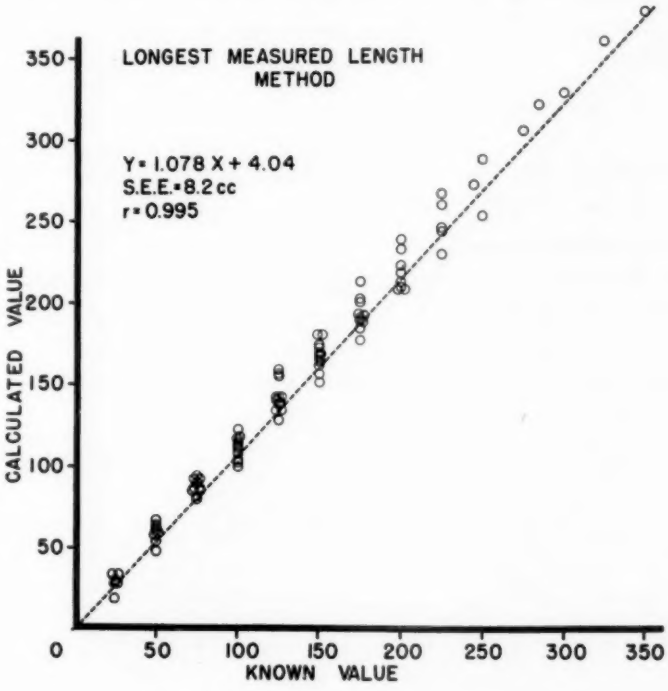

Fig. 6.

Method III (*three measured lengths method*): Three separate diameters are measured from the films, corrected for nonparallel x-ray distortion, and then substituted into an ellipsoid formula to determine chamber volume. The following data are measured from the A-P and lateral films: $1'_o$, length of the outflow tract, in cm. (apex to mid-aortic valve length); $1'_i$, length of the inflow tract, in cm. (apex to mid-mitral valve length); and d'_a, d'_l, largest diameters perpendicular to the inflow tract, in cm., in the respective A-P and lateral films. The primed lengths represent measurements corrected for nonparallel x-rays beams by means of an average correction factor, as previously described. $1'_o$ and $1'_i$ are the largest values for the inflow and outflow tracts, regardless of whether they occur in the A-P or lateral films:

$$V = 4/3\,\pi \cdot 1'/2 \cdot d_1'/2 \cdot d_a'/2 \tag{14}$$

When the measurements of the outflow tract were used as the length of the major axis in the calculation of volume, the calculated volumes greatly exceeded the measured volumes. Empirically, it was found that a value for 1′ derived as an average, $\frac{1'o + 1'i}{2}$, gave calculated volumes that agreed more closely with measured volumes. Fig. 7 shows the relation of the calculated to known volumes for this method.

Method IV (area product method): This method employs the product of the areas of the images measured by planimetry, as suggested by Chapman and co-workers.[5] The known values at each level are related empirically to the area product by a regression equation from which the heart volumes can be calculated directly or read graphically. By the application of this method, the following relation was found:

$$log\ Y = 0.7762\ log\ X - 0.405 \tag{15}$$

where Y = volume, in cm.^{3}, and X = product, in cm.^{4}, of the areas, in cm.^{2}. The results of this method are presented in Fig. 8.

Method V (Simpson's rule): This is a method for calculating chamber volumes by dividing the biplanar images into equal segments and summing the calculated segment volumes as described by Larsson and Kjellberg[8] and Chapman and co-workers.[5] In the present study, this method was applied to 34 observations on 2 postmortem hearts placed in differing positions and rotations.

Volumes were calculated as follows:

$$V = \frac{\pi\ h'}{3}\left[\sum^{odd} a_i'\,1_i' + \sum^{even} \frac{a_j'\,1_j'}{2}\right] \tag{16}$$

$$i = 1, 3, 5, \ldots\ (odd)$$
$$j = 2, 4, 6, \ldots\ (even)$$

where V = volume, in cm.^{3}; h′ = segment lengths corrected for nonparallel x-ray distortion by an average correction factor, as previously described; and a′, 1′ = respective A-P and lateral measured diameters, corrected for nonparallel x-ray distortion by a correction factor determined from the mid-point of each measured diameter. Each image was divided into 20 equal segments which measured 2 mm. to 5 mm. in thickness.

The relationship between calculated and known volumes by this method is expressed by

$$Y = 0.849\,X - 3.92 \tag{17}$$

where Y = known volume, in cm.^{3}, and X = calculated volume, in cm.^{3}, with a S.E.E. of 7.2 c.c. For the same 34 observations the S.E.E. for Method I was 6.9 c.c.; for Method II it was 5.2 c.c., and for Method IV it was 18.2 c.c.

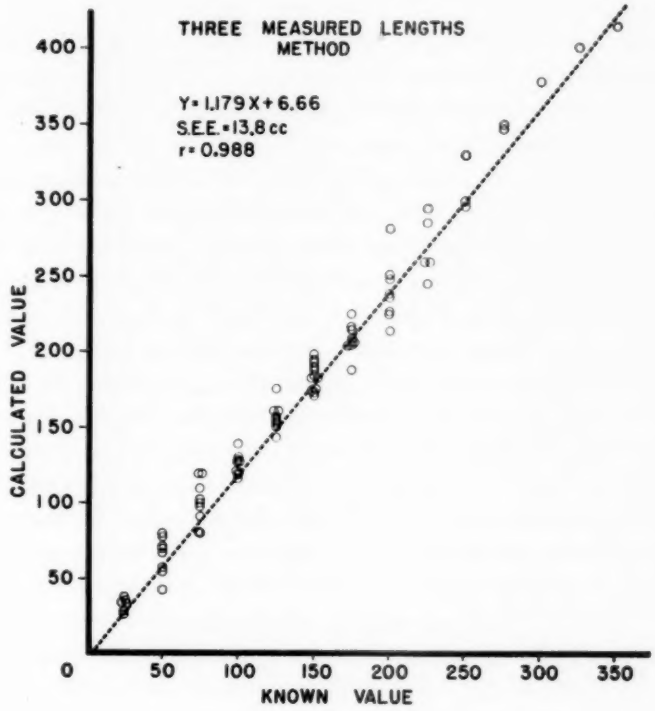
THREE MEASURED LENGTHS
METHOD
Y = 1.179X + 6.66
S.E.E. = 13.8 cc
r = 0.988
CALCULATED VALUE
KNOWN VALUE
0
50
100
150
200
250
300
350
400

Fig. 7.

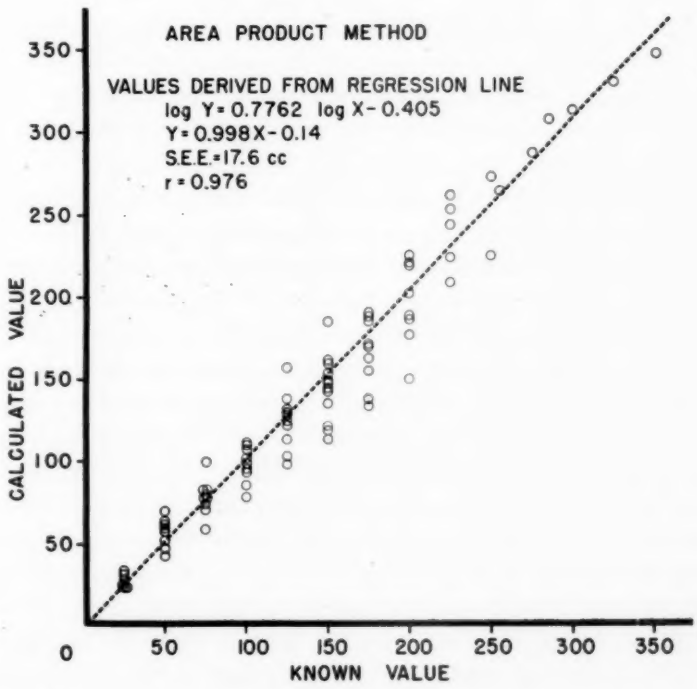
AREA PRODUCT METHOD
VALUES DERIVED FROM REGRESSION LINE
log Y = 0.7762 log X - 0.405
Y = 0.998X - 0.14
S.E.E. = 17.6 cc
r = 0.976
CALCULATED VALUE
KNOWN VALUE
0
50
100
150
200
250
300
350

Fig. 8.

DISCUSSION

These studies demonstrate a relatively simple and accurate method for correction of image magnification and distortion due to proximity of the x-ray tubes in biplane angiocardiography, when films are recorded at right angles. This correction is accomplished for any point identifiable in both x-ray projections by knowing the distance of each x-ray tube to its respective x-ray film, and, finally, the relationship of the given point to the central beam of each x-ray tube. The latter is readily determined from each film by recording the position of the central beam of each x-ray tube as a radiopacity by means of a small lead marker placed on each cassette face. Through knowledge of the above relationships, it is possible to calculate the distance of the given point from each film. The correction factor for each film is a ratio of the object-to-film and tube-to-film distances; the latter can be set as a fixed constant for the equipment used. This method also permits one to locate a point in space and calculate the true length and spatial angle of any straight line, providing that the points that determine the line can be identified on each film. This can be applied to calculate the length and spatial direction of the long axis of the opacified left ventricular chamber, when the aortic valves and apex are visible on each film.

Other investigators, by assuming a geometric reference figure, have calculated individual cardiac chamber volumes from biplane angiocardiographic films.[5,10] Some have corrected for x-ray distortion in making these calculations of volume.[5,10] In the present studies, five methods for calculating left ventricular chamber volumes were tested by relating calculated to known chamber volumes in postmortem hearts. Four of the methods assume that the left ventricular chamber can be represented by an ellipsoid geometric reference figure and involve differing ways of determining the major and minor axes of the left ventricle. The fifth method assumes that the product of the areas in the two projections can be related to the true volumes by means of a regression equation. With each of these methods for calculating ventricular chamber volume, it is important to correct all measurements for distortion due to nonparallel x-rays. In the calculations of volume, errors due to this distortion will be cubed in four of the methods and magnified to the fourth power in the area product method. Study of models and postmortem hearts demonstrated that the lengths of the minor axes, or transverse diameters, are altered far less than the projection of the major, or long axis, which may be considerably foreshortened by different rotations and positions of the left ventricle. Method III (where measurements of the axes are taken directly from the films) and Method IV (area product method) only partially correct for distortion of the long axis of the left ventricle due to differences in projection. This probably accounts for the larger standard error of estimate of these two methods. Furthermore, precise measurement of the transverse diameters in Method III is difficult because of irregularity of the inner wall of the left ventricle.

The spatial and the longest measured length methods and Simpson's rule, a method which compensates for segmental change in the major and minor axes of the images of the ventricular chamber, have similar standard errors of estimates that were substantially lower than those of the other two methods. A

limited number of observations were calculated by the method of Simpson's rule because of the tedium and time consumption involved in applying this method to these data. There is a major degree of tedium involved in all methods of calculation, with the spatial method being the most complicated of all the methods.

As demonstrated by the clay models, the spatial method is theoretically more accurate than the longest measured length method. In the longest measured length method it is assumed that the maximum measured length of the left ventricular chamber in one of the projections will approach the length of the true major axis or apex to aortic valve length, regardless of position or rotation. Data derived from the rotation of postmortem hearts and clay models showed that this method underestimates the length of the long axis of the left ventricle with certain changes in left ventricular projection. The spatial method corrects for this foreshortening of the major axis, as demonstrated by the clay models; however, it should be pointed out that the spatial method is accurate only when the apex and aortic valves can be identified on both the A-P and lateral films. In this regard the postmortem material used in these studies had some shortcomings, because the precise location of the aortic valves and apex were often difficult to determine because of the marked opacification produced by the barium sulfate paste. This difficulty was reflected in the results of the postmortem studies, in which the standard error of estimate for the spatial method was slightly greater than for the longest measured length method. In clinical angiocardiography, where the apex and aortic valves are usually readily identified, particularly when selective left ventricular injection is used, the spatial method for calculating left ventricular chamber volume is undoubtedly more accurate than is the longest measured length method. The spatial method has two other virtues: first, there is an internal check because the X-axis is common to both projections, and, accordingly, the projected apex to aortic valve distance on the X-axis should be equal on both films; second, it provides a means of determining the length and spatial direction of the long axis of the left ventricular chamber, which previously has not been possible.

The chamber volumes as calculated by all of the methods in this study were consistently larger than the known volumes, with a systematic error as expressed by the regression equations of Fig. 5 through 8 and under Method V. Larger calculated volumes, determined by applying Simpson's rule, were also found by Chapman and co-workers.[5] This may be due to the type of reference figure selected to represent the left ventricular chamber. Also, it might be due to the methods used in determining the axes of the reference figure, which applies most directly to the three measured lengths method. As pointed out by Jonsell[7] in using directly measured diameters for calculating total heart volume, the measured diameters may not divide each other into equal parts and may form an oblique angle; therefore, their use is an approximation. Finally, the larger calculated volumes may be due in part to the portion of the left ventricular chamber occupied by trabeculae, papillary muscles, and chordae tendineae.

These studies provide and evaluate methods for calculating volume and changes in volume of the opacified left ventricular chamber of man. When current

angiocardiographic techniques and rapid biplane filming are used, this study establishes a basis for quantifying left ventricular volume and changes in volume in diagnostic and physiologic studies in man.

SUMMARY

1. A method for correcting distortion due to nonparallel x-rays, as applied to biplane angiocardiography, is described.

2. Five methods for calculating left ventricular chamber volumes from biplane x-rays are described and evaluated by clay models and observations on 9 postmortem hearts in which the left ventricular chambers were distended with known volumes of contrast material.

3. The relation of calculated to known left ventricular chamber volumes for these five methods is presented.

4. These methods provide a basis for calculating the volume of the opacified left ventricular chamber as visualized by biplane angiocardiography.

REFERENCES

1. Robb, G. P., and Steinberg, I.: Visualization of the Chambers of the Heart, the Pulmonary Circulation and Great Vessels in Man, Am. J. Roentgenol. **41**:1, 1939.
2. Lind, J., and Wegelius, C.: Angiocardiographic Studies in Children, Advances Pediat. **5**:154, 1952.
3. Soloff, L., Zatuchni, J., Stauffer, H., and Kelly, E.: Angiocardiographic Observations of Intracardiac Flow in the Normal and in Mitral Stenosis, Circulation **13**:334, 1956.
4. Dodge, H. T., and Tannenbaum, H. L.: Left Ventricular Volume in Normal Man and Alterations With Disease (Abstract), Circulation **14**:927, 1956.
5. Chapman, C. B., Baker, O., Reynolds, J., and Bonte, F. J.: Use of Biplane Cinefluorography for Measurement of Ventricular Volume, Circulation **18**:1105, 1958.
6. Liljestrand, G., Lysholm, E., and Zackrisson, C.: Normal Heart Volume in Man, AM. HEART J. **17**:406, 1939.
7. Jonsell, S.: Method for the Determination of Heart Size by Teleroentgenography (A Heart Volume Index), Acta radiol. **20**:325, 1939.
8. Larsson, H., and Kjellberg, S. R.: Roentgenological Heart Volume Determination, With Special Regard to Pulse Rate and Position of the Body, Acta radiol. **29**:159, 1948.
9. Friedman, C. E.: Heart Volume, Myocardial Volume and Total Capacity of the Heart Cavities in Certain Chronic Heart Diseases, Acta med. scandinav. **140**: (Suppl. 157), 1951.
10. Arvidsson, H.: Angiocardiographic Observations in Mitral Disease, With Special Reference to the Volume Variations in the Left Atrium, Acta radiol., Suppl. 158, 1958.

Investigation of the Mechanism of the Hemodynamic Effects of Ganglionic Blockade Produced by Mecamylamine

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Preceding investigations have demonstrated, in general, a decrease in cardiac output and an increase in peripheral resistance after the administration of ganglionic blocking agents.[1-3] Mecamylamine has been shown to have hemodynamic effects similar to ganglionic blocking agents used previously.[4] It has not been established, however, whether the effects of these agents are due purely to the reduction in cardiac filling pressure secondary to peripheral pooling of blood,[3-5] or whether additional factors, such as a decreased discharge from the sympathetic nervous system, are significant as a mechanism of the decreased output.[6] Submersion of the human subject in water after the administration of hexamethonium bromide restored the arterial blood pressure nearly to control values, but no data on cardiac output was recorded during this experiment.[7] In the dog heart-lung preparation or isolated papillary muscle strip, hexamethonium produces an increased force of myocardial contraction; hence, it seems that a direct depressant effect on the myocardium is not likely from this agent.[8,9] Mecamylamine, on the other hand, is reported to decrease contractility of heart muscle strips in vitro.[10] The present report describes a series of experiments designed to test the hemodynamic effect of increasing the central venous pressure after the production of ganglionic blockade.

MATERIAL AND METHODS

Fifteen mongrel dogs were anesthetized with morphine sulfate, 3 mg./Kg. given subcutaneously, followed in 1 hour by sodium pentobarbital, 12 mg./Kg. intravenously. All pressures were recorded with Statham strain gauges and the Sanborn Poly-Viso, with mean pressures determined by electrical integration. Expired air was collected in the Tissot spirometer via a cuffed endotracheal tube and analyzed for oxygen and carbon dioxide by means of the Scholander apparatus. Analyses of blood gas were made by means of the Van Slyke-Neill apparatus. General techniques and formulae used have been previously described.[2] Mecamylamine was administered intravenously in a dose of approximately 1 mg./Kg. of body weight, and the experimental study

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was made when the cardiovascular response seemed stable. This dose has been shown previously to be effective.[4] Arterial pressures were recorded through Cournand needles inserted percutaneously into the femoral artery. Central venous pressure was measured by a cardiac catheter in the right atrium. Statistical comparisons were done by the t-test.

Three sets of experiments were undertaken. First, an attempt was made to evaluate the effect of supporting the central venous pressure by submerging the dog in a tank of water at body temperature. In order to evaluate the effect of submersion, cardiac output was measured four times in each dog. One determination of cardiac output served as a control with the animal supine on a dog board in the empty water tank, and the others as a control with the animal submerged in water, a drug experiment with the dog submerged in water, and a drug experiment with the animal in an empty water tank. The order of the procedures in the experiment was changed so that although both control studies were done before mecamylamine was given, in half of the experiments the control animal submerged in water was studied first, and in half the unsubmerged control was studied first. Similarly, in half of the experiments the medicated submerged animal was studied third, and in half the medicated nonsubmerged animal was studied third. In the second set of experiments, cardiac output was measured three times. Control studies were done, mecamylamine was given and observations repeated, and then the dogs were infused with saline solution rapidly enough to support the right atrial pressures at or near the control level and the third determination of cardiac output was made. In the third set of experiments, dog blood was infused instead of saline solution. This series of experiments constituted a control observation, a determination of cardiac output after the administration of mecamylamine, and then a determination of cardiac output during transfusion of dog blood with the right atrial pressure elevated to approximately the control level. Transfusion was begun about 5 minutes before the last determination of cardiac output, and blood was run in rapidly through a polyethylene tube which had an internal diameter of about 1.5 mm. The rate of administration throughout the determination of cardiac output was adjusted to maintain the right atrial pressure near the control levels. In a few of these transfusion experiments, after an initial satisfactory response to transfusion, there was a sudden decrease in arterial pressure and right atrial pressure which required a large volume of blood to bring the dog back to the control state; these experiments were discarded on the assumption that there may have been reactions to the infused blood.[11] In the series of 5 experiments with transfusion of blood, no such reaction was encountered and the data are believed to be acceptable.

RESULTS

Results are summarized for the experiments involving submersion of the dog in water in Table I. When the animals were submerged in water, the right atrial mean pressure rose significantly ($p < 0.001$), and although it decreased somewhat after the administration of mecamylamine, the pressure remained higher in the right atrium throughout the determination of the cardiac output after the administration of mecamylamine and during submersion than it did in the control study. After the administration of mecamylamine, and when the water was drained out of the tank, the right atrial pressure fell considerably and remained lower than it had been during the control observation in air ($p < 0.02$). Changes in the blood pressure of the pulmonary artery were similar, in general, to those just described for the right atrium. The mean systemic arterial blood pressure rose slightly but not significantly with submersion, was unchanged after the administration of mecamylamine as long as the animal was submerged, and decreased, but not significantly, as compared to the control when the water was drained from the tank. Submersion in water did not change the arterial hemoglobin; however, the administration of the drug was accompanied by a decrease in hemoglobin, and this was confirmed by a decrease in the hematocrit.

The control cardiac output did not change significantly with submersion. It decreased slightly but not significantly after the administration of mecamylamine and during submersion; however, when the animal was not submerged, cardiac output was significantly reduced ($p < 0.02$). Right ventricular work was reduced significantly after the administration of mecamylamine, both before and after the removal of the water. Left ventricular work remained unchanged while the animal was submerged in water, but when the water was drained out of the tank, the left ventricular work was decreased ($p < 0.05$). After administration of the drug the total peripheral resistance did not change significantly while the animal was submerged in water; however, when the water was drained away, the peripheral resistance rose significantly ($p < 0.02$). Total pulmonary resistance did not change appreciably at any time during the experiment.

In Table II, data are given from the second set of experiments, conducted on 4 dogs. These data consist of control observations, data after administration of mecamylamine, and then results subsequent to the administration of mecamylamine but while the right atrial pressure was supported by infusion of saline. The cardiac rate increased after the administration of mecamylamine ($p < 0.01$), and although it declined somewhat during the administration of saline, it remained significantly elevated ($p < 0.02$). Arterial pressure decreased slightly after the drug had been given ($p < 0.2$) but increased again during infusion of saline ($p < 0.05$), whereas both pulmonary arterial and right atrial pressure decreased significantly after mecamylamine and increased significantly after infusion of saline. The arteriovenous oxygen difference tended to increase after the administration of mecamylamine but decreased more significantly ($p < 0.02$) during the infusion of saline. Changes in the hematocrit were very small until the administration of saline solution, and then the hematocrit became significantly lower ($p < 0.02$). Cardiac output tended to decrease after the administration of mecamylamine but increased significantly with the infusion of saline ($p < 0.01$). The total peripheral resistance was variable but fell during the administration of saline ($p < 0.05$). Left ventricular and right ventricular work decreased slightly after the administration of mecamylamine but increased above the control values during the infusion of saline ($p < 0.01$).

In the third set of experiments in which the transfusion of blood instead of saline solution was used to increase central venous pressure after mecamylamine (see Table III), there were 5 satisfactory studies. The cardiac rate in these animals increased after mecamylamine ($p < 0.01$) but decreased again during the administration of blood. Systemic arterial pressure was variable, but tended to fall after the administration of mecamylamine and to rise while blood was being transfused; in neither case was the change significant. The pulmonary arterial pressure tended to fall after mecamylamine but was significantly increased again by transfusion of blood ($p < 0.01$). The right atrial mean pressure decreased significantly with the drug ($p < 0.02$) and increased again with transfusion ($p < 0.01$). The arteriovenous oxygen difference increased after the administration of mecamylamine ($p < 0.05$) and tended to decrease again during the administration of blood ($p < 0.4$). The hematocrit was essentially unchanged.

TABLE I. EXPERIMENTS IN 6 DOGS

	C_A*	C_{H_2O}†	D_{H_2O}‡	D_A§	p VALUE FOR COMPARISON			
					$C_A - C_{H_2O}$	$C_A - D_{H_2O}$	$C_A - D_A$	$C_{H_2O} - D_{H_2O}$
Heart rate	92	99	113	114	<0.2	<0.01	<0.01	<0.1
Mean systemic arterial blood pressure (mm. Hg)	94	100	99	92	<0.2	<0.4	<0.8	<0.9
Mean pulmonary arterial blood pressure (mm. Hg)	14	16	10	7	<0.1	<0.01	<0.01	<0.01
Mean right atrial blood pressure	1.7	4.3	2.8	−0.4	<0.001	<0.01	<0.02	<0.05
Oxygen consumption (ml./min.)	117	127	112	109	<0.05	<0.4	<0.05	<0.05
Body respiratory quotient	0.80	0.84	0.89	0.82	<0.2	<0.01	<0.2	<0.05
Arteriovenous oxygen difference (ml./100 ml. blood)	3.6	3.6	3.9	4.6	<0.9	<0.4	<0.1	<0.5
Arterial hemoglobin (Gm./100 ml.)	13.9	13.7	12.3	12.4	<0.4	<0.001	<0.01	<0.01
Arterial hematocrit (%)	42	42	39	39	<0.9	<0.01	<0.02	<0.2
Cardiac output (L./min.)	3.5	3.7	3.1	2.4	<0.4	<0.2	<0.02	<0.2
Left ventricular work (Kg.M./min.)	4.5	5.2	4.2	3.1	<0.2	<0.2	<0.05	<0.2
Right ventricular work (Kg.M./min.)	0.7	0.8	0.5	0.3	<0.1	<0.02	<0.01	<0.05
Total peripheral resistance (dynes cm.$^{-5}$/sec.)	2,131	2,151	2,797	3,076	<0.9	<0.1	<0.02	<0.2
Total pulmonary resistance (dynes cm.$^{-5}$/sec.)	324	360	277	240	<0.2	<0.1	<0.2	<0.1

*Control observation—dog at atmospheric pressure.
†Control observation—dog submerged in water.
‡Experimental observation—dog submerged in water and under influence of mecamylamine.
§Experimental observation—dog at atmospheric pressure and under influence of mecamylamine.

TABLE II. EXPERIMENTS IN 4 DOGS

	CONTROL*	DRUG†	INFUSED‡	C–D§	D–I‖	C–I¶
Heart rate	72	136	114	<0.01	<0.1	<0.02
Mean systemic arterial blood pressure (mm. Hg)	117	93	116	<0.2	<0.05	<0.9
Mean pulmonary arterial blood pressure (mm. Hg)	15	10	18	<0.02	<0.05	<0.3
Mean right atrial blood pressure (mm. Hg)	3.0	0.7	3.3	<0.05	<0.05	<0.7
Oxygen consumption (ml./min.)	90	83	92	<0.2	<0.02	<0.8
Body respiratory quotient	0.80	0.86	0.76	<0.1	<0.1	<0.3
Arteriovenous oxygen difference (ml./100 ml. blood)	4.2	5.4	2.9	<0.3	<0.02	<0.05
Arterial hematocrit (%)	48.0	47.5	38.3	<0.9	<0.02	<0.02
Cardiac output (L./min.)	2.2	1.7	3.5	<0.2	<0.01	<0.1
Left ventricular work (Kg.M./min.)	3.5	2.2	5.6	<0.05	<0.01	<0.2
Right ventricular work (Kg.M./min.)	0.4	0.2	0.9	<0.1	<0.05	<0.2
Total peripheral resistance (dynes cm.$^{-5}$/sec.)	4,323	4,635	2,821	<0.6	<0.05	<0.02
Total pulmonary resistance (dynes cm.$^{-5}$/sec.)	537	496	425	<0.6	<0.4	<0.1

*Control observations.
†Observations after establishing ganglionic blockade by mecamylamine.
‡Repeat observations after administration of mecamylamine and during infusion of saline.
§Statistical comparison of the control study with that after mecamylamine.
‖Statistical comparison of the study after mecamylamine with that during infusion of saline.
¶Statistical comparison of the control study with that after mecamylamine and during infusion of saline.

TABLE III. EXPERIMENTS IN 5 DOGS

	CONTROL*	DRUG†	TRANSFUSED‡	C–D§	D–T‖	C–T¶
Heart rate	86	134	108	<0.01	<0.1	<0.3
Mean systemic arterial blood pressure (mm. Hg)	115	109	131	<0.4	<0.2	<0.4
Mean pulmonary arterial blood pressure (mm. Hg)	15	12	21	<0.1	<0.01	<0.01
Mean right atrial blood pressure (mm. Hg)	1.1	−0.3	3.3	<0.02	<0.01	<0.05
Oxygen consumption (ml./min.)	96	91	94	<0.4	<0.7	<0.7
Body respiratory quotient	0.86	0.85	0.92	<0.9	<0.05	<0.3
Arteriovenous oxygen difference (ml./100 ml. blood)	3.7	5.2	4.5	<0.05	<0.4	<0.2
Arterial hematocrit (%)	43	41	43	<0.4	<0.5	<0.9
Cardiac output (L./min.)	2.7	1.8	2.2	<0.01	<0.3	<0.2
Left ventricular work (Kg.M./min.)	4.3	2.6	4.1	<0.1	<0.2	<0.9
Right ventricular work (Kg.M./min.)	0.5	0.3	0.6	<0.001	<0.2	<0.5
Total peripheral resistance (dynes cm.$^{-5}$/sec.)	3,528	5,011	5,107	<0.001	<0.9	<0.2
Total pulmonary resistance (dynes cm.$^{-5}$/sec.)	467	568	827	<0.2	<0.2	<0.1

*Control study.
†Study after administration of mecamylamine.
‡Study after administration of mecamylamine and during transfusion of blood.
§Statistical comparison of control study with that after administration of mecamylamine.
‖Statistical comparison of study after mecamylamine with that after mecamylamine and during transfusion of blood.
¶Statistical comparison of control study with that after administration of mecamylamine and during transfusion of blood.

The cardiac output fell with the administration of mecamylamine ($p < 0.01$) but returned toward control values during the infusion of blood. Total peripheral resistance rose with the administration of mecamylamine ($p < 0.001$), and during the transfusion of blood it remained increased. Left ventricular work and right ventricular work tended to decrease after the administration of mecamylamine and to increase again toward normal during transfusion of blood.

DISCUSSION

The first set of experiments in this series showed that if the animal was submerged supine in water at body temperature, the central venous pressure was supported and the hemodynamic effects of mecamylamine tended to be reduced. Thus, the arterial hypotension, decrease in central venous pressure, and reduction in cardiac output were all partially corrected. This reduced effect from mecamylamine was presumably due to the fact that the diffuse, even pressure of the water applied to the dog's body prevented peripheral or visceral pooling of blood by supporting the venous return into the central circulatory system. It was observed, however, that when the animal was submerged in water, the pressure within the esophagus rose in the same manner as did the right atrial pressure; therefore, it was considered that intrathoracic pressure increased generally and the effective distending force in the right atrium might not be restored adequately. Consequently, the other two series of experiments in which right atrial pressure was maintained by infusion of saline and blood were undertaken.

Infusion of physiologic saline solution seemed to be a simple and direct approach toward restoration of central venous pressure, and, in general, the hemodynamic effects of mecamylamine were reversed by the rapid infusion of saline. However, the considerable drop in the arterial hematocrit and the decrease in arteriovenous oxygen difference produced by the required quantity of saline solution raised the question of how much of the reversal of hemodynamic effects obtained was due to induction of hydremia and how much might be truly attributed to re-establishment of an effective filling pressure in the heart. Therefore, the third set of experiments using the transfusion of blood were undertaken. In general, when the central venous pressure was supported by blood, the hemodynamic effects of mecamylamine were reversed. Hence, all of the experiments tended to agree.

It is well known that in the intact dog, Starling's law does not strictly apply and the filling pressure is not the only factor which controls cardiac output.[12] Furthermore, there is evidence that blocking of the sympathetic nerve endings reduces cardiac output and coronary blood flow, and produces hemodynamic changes very similar to those of the ganglionic blocking drugs.[13] Whereas both of these sets of observations appear to be pertinent to this study, it would seem that the present data may be interpreted most reasonably as indicating that, under the conditions of these experiments, the reduced central filling pressure is one of the major factors responsible for the hemodynamic effects of mecamylamine.

CONCLUSIONS

1. In a series of dogs given the ganglionic blocking drug, mecamylamine, an attempt has been made to evaluate the effect of supporting the central venous pressure by various means.

2. When the central venous pressure is supported by submerging the dog in water, by infusion of saline, or by transfusion of blood, the hemodynamic effects of mecamylamine are to some extent reversed.

3. Decreased central venous pressure appears to be responsible to some extent for the hemodynamic effect of mecamylamine.

REFERENCES

1. Werkö, L., Wade, G., Frisk, A. R., and Eliasch, H.: The Effect of Hexamethonium Bromide in Arterial Hypertension, Lancet **2**:470, 1951.
2. Crumpton, C. W., Rowe, G. G., O'Brien, G., and Murphy, Q. R.: The Effect of Hexamethonium Bromide Upon Coronary Flow, Cardiac Work, and Cardiac Efficiency in Normotensive and Renal Hypertensive Dogs, Circulation Res. **2**:79, 1954.
3. Crosley, A. P., Jr., Brown, J. F., Tuchman, H., Crumpton, C. W., Huston, J. H., and Rowe, G. G.: The Acute Hemodynamic and Metabolic Response of Hypertensive Patients to Pentolinium Tartrate, Circulation **14**:584, 1956.
4. Rowe, G. G., Castillo, C. A., Maxwell, G. M., White, D. H., Jr., Freeman, D. J., and Crumpton, C. W.: The Effect of Mecamylamine on Coronary Flow, Cardiac Work and Cardiac Efficiency in Normotensive Dogs, J. Lab. & Clin. Med. **52**:883, 1958.
5. Combes, B., Preedy, J. R. K., Wheeler, H. O., Hays, R. M., and Bradley, S. E.: The Hemodynamic Effects of Hexamethonium Bromide in the Dog, With Special Reference to "Splanchnic Pooling," J. Clin. Invest. **36**:860, 1957.
6. Cotten, M. De V., Brown, J. M., and Kronen, P. S.: Heart Force Responses to Pressor Amines During Hypotension Produced by Hexamethonium, Anesthesiology **15**:126, 1954.
7. Restall, P. A., and Smirk, F. H.: Regulation of Blood Pressure Levels by Hexamethonium Bromide and Mechanical Devices, Brit. Heart J. **14**:1, 1952.
8. Lee, W. C., and Shideman, F. E.: Inotropic Action of Hexamethonium, Circulation Res. **6**:66, 1958.
9. Paton, W. D. M., and Zaimis, E. J.: The Methonium Compounds, Pharmacol. Rev. **4**:219, 1952.
10. Bennett, G., Tyler, C., and Zaimis, E.: Mecamylamine and Its Mode of Action, Lancet **2**:218, 1957.
11. Bliss, J. Q., Johns, D. G., and Burgen, A. S. V.: Transfusion Reactions Due to Plasma Incompatability in Dogs, Circulation Res. **7**:79, 1959.
12. Rushmer, R. F., Smith, O., and Franklin, D.: Mechanism of Cardiac Control in Exercise, Circulation Res. **7**:602, 1959.
13. Rowe, G. G., Castillo, C. A., Clifford, J. E., Maxwell, G. M., and Crumpton, C. W.: Hemodynamic Effects of SKF 6890, The Pharmacologist **1**:69, 1959.

Quinidine Intoxication: An Experimental Study of the Effect of Molar Sodium Lactate and Potassium Chloride

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There has been recent interest in the possible beneficial effects of molar sodium lactate in the treatment of quinidine toxicity in both man and experimental animals.[1-6]

Following the infusion of molar sodium lactate, almost immediate reversal of quinidine cardiotoxicity has been reported.[1-6] This reversal was manifested by a decrease in QRS duration, abolition of ventricular tachycardia or idioventricular rhythm, increase in blood pressure, and correction of acidosis which had followed the administration of quinidine.

Bellet and others[1,5] also showed a concomitant decrease in plasma quinidine and concentration of potassium, and an increase in the concentration of plasma sodium after molar sodium lactate had been given. Wasserman and associates[4] stated that no significant changes in serum sodium, potassium, chloride, calcium, phosphorus, and magnesium were observed immediately after giving quinidine, immediately after cessation of sodium lactate therapy, and during a 15- to 20-minute period of observation following the infusion of molar sodium lactate. However, a significant decrease in arterial blood pH and plasma bicarbonate was demonstrated following intravenous administration of quinidine. After the intramuscular injection of quinidine for 5 to 7 days, Gertler and co-workers[7] reported a gain in intracellular cardiac potassium and a decrease in intracellular cardiac sodium.

Because of electrocardiographic similarities between hyperpotassemia and quinidine intoxication, it has been suggested that hyperpotassemia may play an important role in quinidine intoxication.[4,5]

We have studied the relationship of molar sodium lactate and potassium chloride to quinidine intoxication, and the influence of quinidine on plasma potassium, levels of sodium, and the pH of arterial blood. Observations were made with respect to levels of plasma quinidine as related to infusions of molar sodium lactate and potassium chloride.

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MATERIAL AND METHODS OF STUDY

Thirty-six dogs, which weighed 7 to 13 kilograms, were anesthetized with 25 to 35 mg. per kilogram of Nembutal given intravenously. Endotracheal intubation was performed and respiration was maintained with a Phipps-Bird type respirator.

One femoral artery was cannulated and used for continuous recording of the blood pressure. A catheter was inserted into the other femoral artery and blood samples were drawn for the determination of blood pH, plasma quinidine, and concentration of potassium and sodium. A Sanborn Poly-Viso recorder was used for recording of a continuous electrocardiogram (Standard Leads I and II) and arterial blood pressure. The determination of blood pH was carried out with a Leeds and Northrup line operated pH meter at body temperature. A Patwin Model FC flame photometer was employed for the determination of plasma potassium and sodium. The determination of plasma quinidine was performed according to the protein precipitation method of Brodie and associates.[8]

The dogs were divided into six groups: Groups 1 and 2 included 8 dogs each; Groups 3, 4, 5, and 6 included 5 dogs each.

Group 1 (quinidine).—After blood samples were drawn for control studies, 20 mg. per kilogram of quinidine gluconate (base) diluted in 20 c.c. of normal saline was administered intravenously at a rate of 2 mg. per kilogram per minute. After injection of quinidine, samples of blood were collected immediately and at intervals of 10, 20, 30, and 60 minutes.

In Groups 1 to 5, the quinidine gluconate was given at a standard rate and dose calculated on a kilogram basis.

Group 2 (quinidine–molar sodium lactate).—Quinidine gluconate was given after the collection of the preliminary blood samples. Samples were drawn after administration of quinidine. Ten minutes after infusion of quinidine, 20 to 40 c.c. of molar sodium lactate was given intravenously at a rate of 5 c.c. per minute. Samples of blood were obtained immediately after this infusion and thereafter as described in Group 1.

Group 3 (molar sodium lactate–quinidine).—After collection of the control blood samples, 20 to 40 c.c. of molar sodium lactate was given at a rate of 5 c.c. per minute. Blood samples were obtained at the end of the infusion. Quinidine gluconate was then given, and blood samples were obtained as described in Group 1.

Group 4 (quinidine–potassium chloride).—After control blood samples were drawn, quinidine gluconate was given. Blood samples were drawn after this infusion. Ten minutes after quinidine had been administered, 10 to 15 mEq. of potassium chloride diluted in 100 c.c. of normal saline was given intravenously within approximately 10 minutes. Blood samples were collected at the end of the infusion of potassium chloride, and thereafter as described in Group 1.

Group 5 (potassium chloride–quinidine).—After control blood samples were drawn, 10 to 15 mEq. of potassium chloride was given in the same manner as in Group 4. Blood samples were taken after the end of the infusion of potassium chloride; quinidine gluconate was given; and blood samples were obtained as with Group 1.

Group 6 (quinidine–molar sodium lactate, repeated doses).—After control blood samples were drawn, quinidine gluconate was given intravenously at a rate of 2 to 3 mg. per kilogram per minute until signs of severe quinidine intoxication developed, that is, marked widening of QRS complex and hypotension. Twenty to forty cubic centimeters of molar sodium lactate was infused intravenously at a rate of 5 c.c. per minute. Repeated infusions of quinidine alternating with molar sodium lactate were given until death. Blood samples were obtained before and after administration of quinidine and molar sodium lactate.

EXPERIMENTAL RESULTS

1. *Levels of Plasma Potassium.*—The mean control levels for plasma potassium in Groups 1, 2, 3, 4, 5, and 6 were 3.5, 3.8, 3.7, 3.4, 3.6, and 3.5 mEq. per liter, respectively. Immediately after intravenous injection of quinidine, there was a definite decrease in plasma potassium. The mean decreases in Groups 1, 2, 4, and 6 were 0.6, 0.8, 0.5, and 0.9 mEq. per liter, respectively.

In Group 2 (quinidine–molar sodium lactate), there was a further decrease in plasma potassium following infusion of molar sodium lactate. The mean decrease was 0.3 mEq. per liter.

In Group 3 (molar sodium lactate–quinidine), there was a decrease in plasma potassium immediately after infusion of molar sodium lactate. The mean decrease was 0.5 mEq. per liter. Following injection of quinidine, there was a further decrease in the concentration of plasma potassium, with a mean decrease of 0.4 mEq. per liter.

In Group 4 (quinidine–potassium chloride), after injection of quinidine, there was an initial decrease in plasma potassium of 0.5 mEq. per liter. The plasma potassium increased from 2.9 to 5.1 mEq. per liter after the subsequent infusion of potassium chloride.

In Group 5 (potassium chloride–quinidine), after infusion of potassium chloride, the mean plasma potassium increased to 5.6 mEq. per liter. Following injection of quinidine, the mean plasma potassium dropped to 4.5 mEq. per liter. The decrease in plasma potassium after injection of quinidine persisted for the 60-minute period of observation (Fig. 1).

In Group 6 (quinidine–molar sodium lactate, repeated doses), the mean plasma potassium dropped from 3.5 to 2.6 mEq. per liter when signs of severe quinidine intoxication appeared. After injection of molar sodium lactate, it dropped to 2.3 mEq. per liter.

Subsequent levels of plasma potassium after repeated infusions of quinidine and molar sodium lactate are shown in Fig. 2.

TABLE I. MEAN CONCENTRATION OF PLASMA POTASSIUM (GROUPS 1-6)

GROUP	PLASMA POTASSIUM CONCENTRATION (MEQ./L.)		
1	Control 3.5	After Q 2.9	
2	Control 3.8	After Q 3.0	After MSL 2.7
3	Control 3.7	After MSL 3.2	After Q 2.8
4	Control 3.4	After Q 2.9	After KCl 5.1
5	Control 3.6	After KCl 5.6	After Q 4.5
6	Control 3.5	After Q 2.6	

Q: Quinidine. MSL: Molar sodium lactate.

2. *Levels of Plasma Sodium.*—There was no significant change in the levels of plasma sodium after injection of quinidine.

3. *Arterial Blood pH.*—The mean control arterial blood pH of Groups 1, 2, 3, 4, 5, and 6 were 7.46, 7.49, 7.45, 7.36, 7.51, and 7.42, respectively. Immediately following infusion of quinidine, there was a decrease in arterial blood pH in Groups 1, 2, 4, 5, and 6, with mean decreases of 0.07, 0.05, 0.04, 0.05, and 0.09, respectively

In Group 3 (molar sodium lactate–quinidine), the mean arterial blood pH was increased to 7.56 after administration of molar sodium lactate, and there was only a slight decrease in arterial blood pH after subsequent administration of quinidine.

In Group 2 (quinidine–molar sodium lactate) and Group 6 (quinidine–molar sodium lactate, repeated doses), the arterial blood pH was raised to or above the control levels following infusion of molar sodium lactate.

Intravenous potassium chloride given in this study had no significant effect on arterial blood pH.

4. *Levels of Plasma Quinidine.*—The maximum concentration of plasma quinidine was noted immediately after the injection of quinidine. In each group, the concentration of quinidine leveled off quickly and dropped to one third to one fourth of the maximum level 60 minutes after the administration of quinidine (Fig. 3).

In Group 3 (molar sodium lactate–quinidine), the concentrations of plasma quinidine were lower than in the other groups.

In Group 6 (quinidine–molar sodium lactate, repeated doses), the mean level of plasma quinidine was 32 mg. per liter when signs of severe quinidine intoxication appeared. After injection of molar sodium lactate, the mean plasma quinidine dropped to 20 mg. per liter. Subsequent levels of plasma quinidine after infusions of quinidine and molar sodium lactate are shown in Fig. 2.

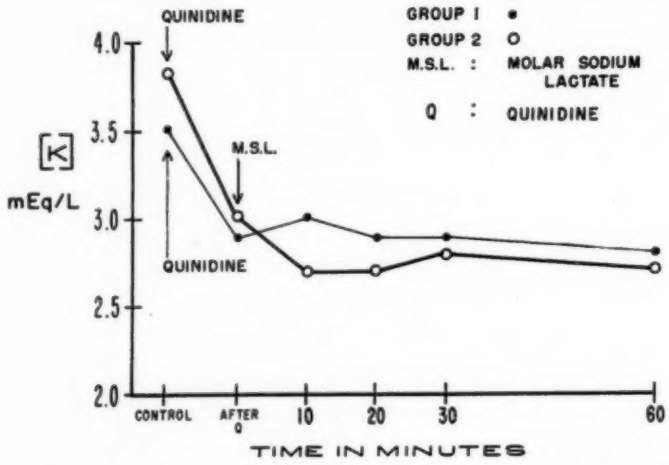

Fig. 1.—Mean concentration of plasma potassium in Groups 1 and 2. After injection of quinidine, there was a fall in the concentration of plasma potassium. There was a further fall in Group 2 after infusion of molar sodium lactate.

5. *Arterial Blood Pressure.*—The mean blood pressure after administration of Nembutal in the present study was 164 mm. Hg systolic and 106 mm. Hg diastolic. In Figs. 4 and 5 are shown the mean blood pressures of Groups 1, 2, 4, and Groups 3 and 5, respectively. The initial response of blood pressure to quinidine was a drop in diastolic pressure with a resultant increase in pulse pressure (Fig. 6). This was followed quickly by a concomitant decrease in systolic and diastolic pressures. The maximum drop in blood pressure usually occurred toward the end of the injection of quinidine. The blood pressure returned toward the control level gradually; however, it remained considerably lower than the control levels in Group 1 (quinidine).

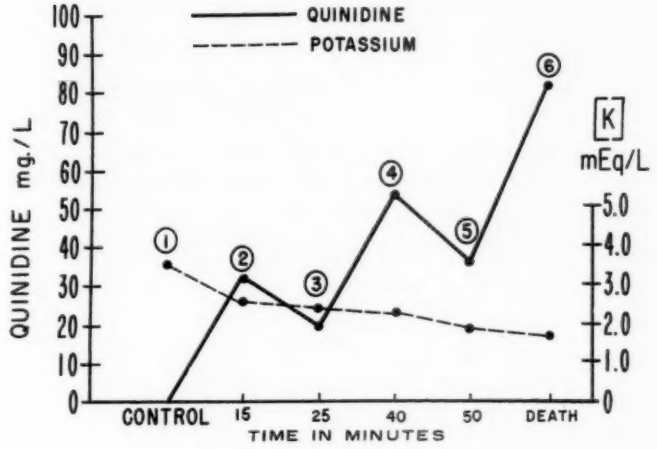

Fig. 2.—Mean levels of plasma potassium and quinidine in Group 6 after repeated doses of quinidine and molar sodium lactate. *1*, Quinidine was given until evidence of severe quinidine intoxication appeared. *2*, Molar sodium lactate was injected. *3*, Quinidine was given again. *4*, Additional injection of molar sodium lactate. *5*, Quinidine was given until the death of animals. *6*, Dogs died at this point.

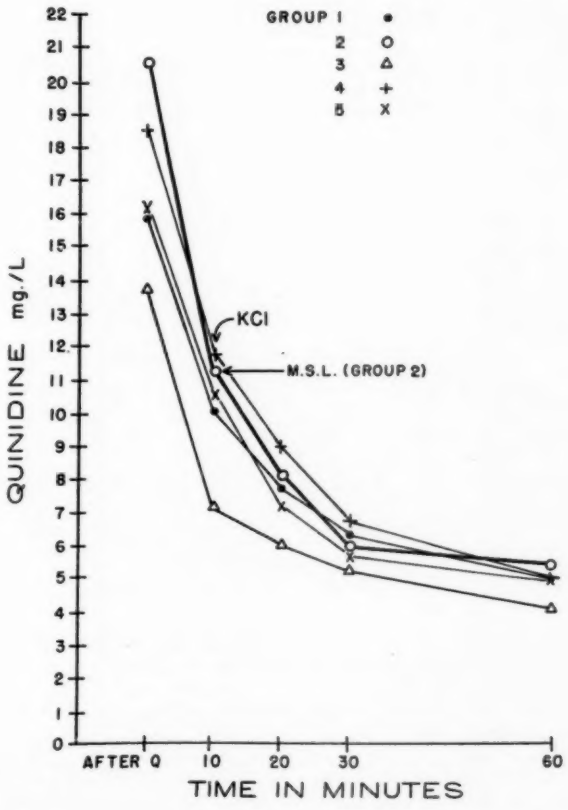

Fig. 3.—Mean levels of plasma quinidine (mg./L.) after injection of quinidine in Groups 1-5. Group 3 had received molar sodium lactate prior to quinidine; Group 5 had received potassium chloride prior to quinidine. Ten minutes after injection of quinidine, Group 2 received molar sodium lactate, and Group 4 received potassium chloride.

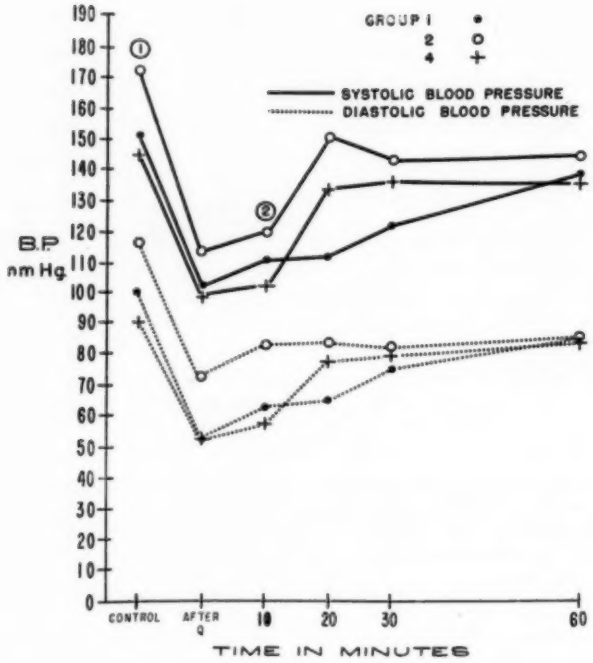

Fig. 4.—Determination of mean blood pressure in Groups 1, 2, and 4. The control levels are shown at *1*; at this point quinidine was given. The fall in blood pressure immediately after injection of quinidine was recorded. After 10 minutes of observation, Group 2 received molar sodium lactate, and Group 4 received potassium chloride at *2*.

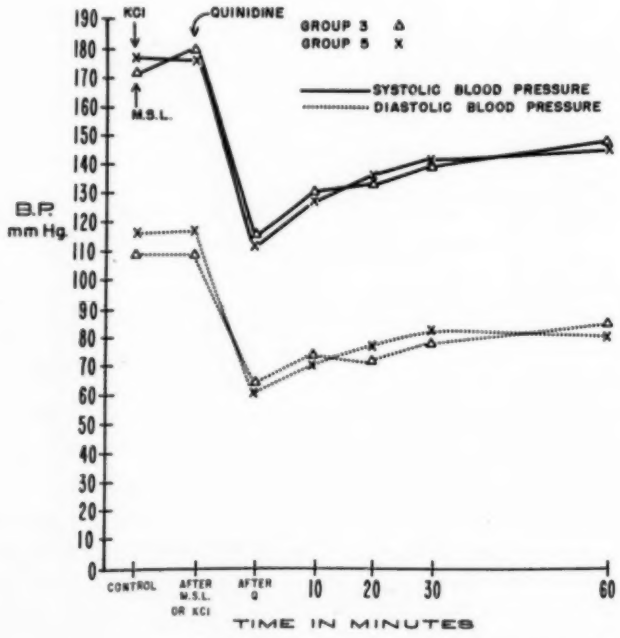

Fig. 5.—Determination of mean blood pressure in Groups 3 and 5. Prior to injection of quinidine, Group 3 received molar sodium lactate, and Group 5 received potassium chloride. The subsequent changes in blood pressure are recorded.

In Group 2 (quinidine–molar sodium lactate), there was a moderate increase in blood pressure in 5 dogs, after injection of molar sodium lactate.

In Group 6 (quinidine–molar sodium lactate, repeated doses), molar sodium lactate had no beneficial effect on blood pressure. In 2 dogs, the blood pressure dropped while molar sodium lactate was being infused (Fig. 7).

Molar sodium lactate when given prophylactically did not prevent the hypotensive effect of quinidine. As is shown in Fig. 5, the decrease in blood pressure was similar to that observed in the dogs of Group 5 which received potassium chloride prior to injection of quinidine.

There was a marked increase in blood pressure in 2 of the dogs of Group 4 (quinidine–potassium chloride) (Fig. 8). There was no decrease in blood pressure coinciding with the increase in pulse rate.

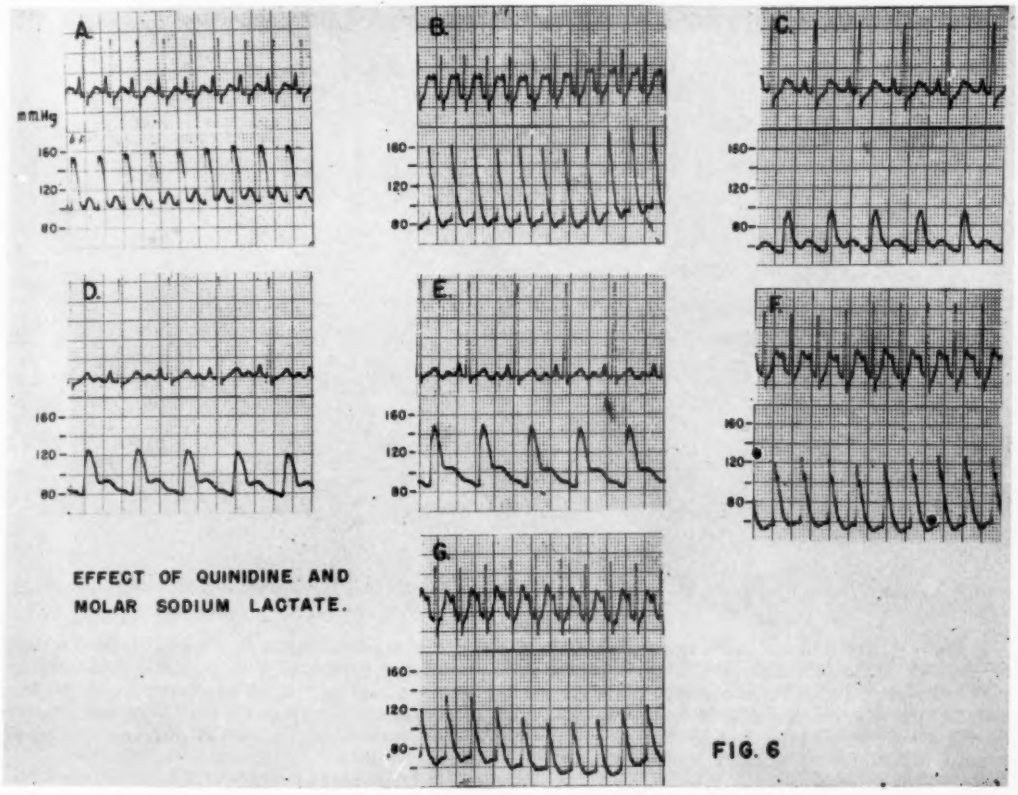

Fig. 6.—Effect of quinidine and molar sodium lactate on the electrocardiogram (Lead II) and blood pressure. *A*, Control. Pulse rate 210/min., QRS 0.04 sec., blood pressure 160/104 mm. Hg, plasma potassium 3.4 mEq./L., pH 7.45. *B*, One minute after the initiation of the injection of quinidine. Pulse rate 250/min., blood pressure 160/80 mm. Hg. Note the increase in pulse rate and drop in diastolic pressure and resultant increase in pulse pressure. *C*, Immediately after injection of quinidine. Pulse rate 129/min., blood pressure 94/56 mm. Hg, plasma potassium 2.7 mEq./L., pH 7.40, plasma quinidine 25 mg./L. *D*, Immediately after 30 c.c. of molar sodium lactate, pulse rate 113/min., blood pressure 122/78 mm. Hg, plasma potassium 2.3 mEq./L., pH 7.46. Note the prominent U wave. *E*, Five minutes after molar sodium lactate. Pulse rate 120/min., blood pressure 144/84 mm. Hg. *F*, Ten minutes after molar sodium lactate. Pulse rate 210/min., blood pressure 124/56 mm. Hg, plasma potassium 2.2 mEq./L., pH 7.43, plasma quinidine 7 mg./L. *G*, Sixty minutes after quinidine (44 minutes after molar sodium lactate). Pulse rate 200/min., blood pressure 120/60 mm. Hg, plasma potassium 2.3 mEq./L., pH 7.45, plasma quinidine 4 mg./L.

6. *Pulse and Electrocardiographic Changes.*—During the first 30-second to 1-minute period of infusion of quinidine, there was a transient increase in pulse rate. This was followed by a gradual decrease to approximately two thirds to one half of the control rate near the end of injection of quinidine (Fig. 6). The pulse rate remained slow for 20 to 30 minutes, and then gradually returned toward the control rate within 60 to 90 minutes.

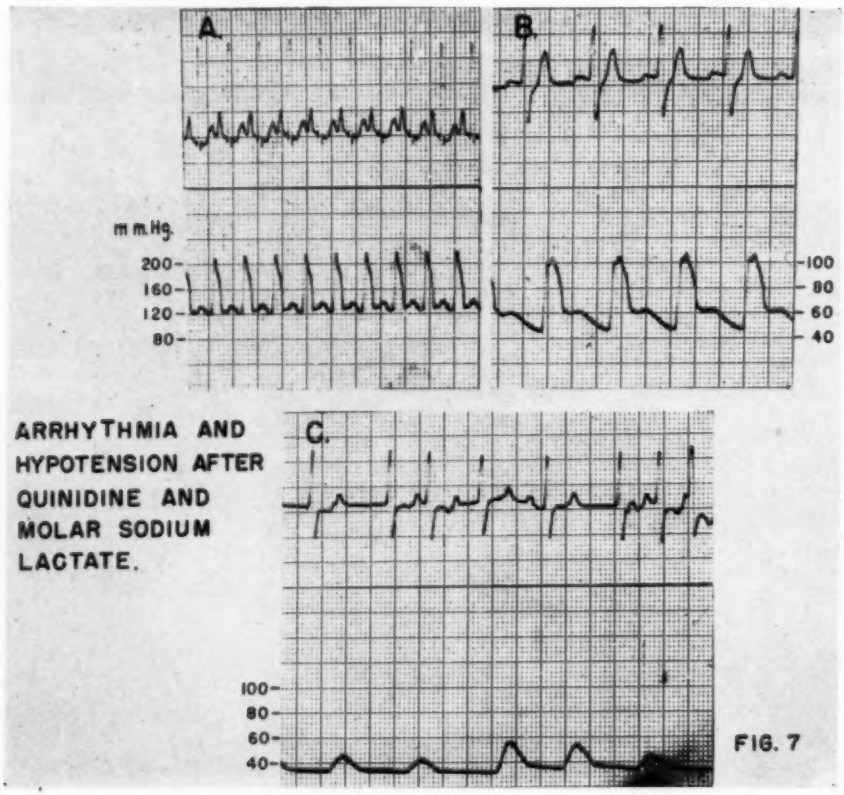

Fig. 7.—Arrhythmia and hypotension after administration of quinidine and molar sodium lactate. *A*, Control. Pulse rate 250/min., QRS 0.04 sec., blood pressure 212/120 mm. Hg, plasma potassium 3.9 mEq./L., pH 7.48. *B*, Immediately after quinidine. Pulse rate 110/min., QRS 0.10 sec., blood pressure 104/48 mm. Hg, plasma potassium 3.3 mEq./L., pH 7.40, plasma quinidine 27 mg./L. *C*, After 20 c.c. of molar sodium lactate. Bizarre nodal arrhythmia and a marked drop in blood pressure developed. Plasma potassium 2.7 mEq./L., plasma quinidine 14 mg./L.

In Group 2 (quinidine–molar sodium lactate), there was a marked increase in pulse rate in 3 dogs, and a slight to moderate increase in rate in the remaining 5 dogs, 5 to 10 minutes after infusion of molar sodium lactate. Molar sodium lactate and potassium chloride given prior to quinidine did not change the rate significantly.

In Group 4 (quinidine–potassium chloride), there was a marked increase in pulse rate in 2 dogs (Fig. 8), and no significant change in the other 3 dogs following infusion of potassium chloride.

In Group 3 (molar sodium lactate–quinidine), 1 dog developed ectopic atrial and ventricular beats after the infusion of 40 c.c. of molar sodium lactate. However, the arrhythmia disappeared immediately after the initiation of the injection of quinidine.

In Group 6 (quinidine–molar sodium lactate, repeated doses), 2 dogs developed bizarre nodal arrhythmia or frequent ectopic ventricular beats which lasted approximately 5 minutes after the injection of molar sodium lactate. This was accompanied by a marked drop in blood pressure (Fig. 7).

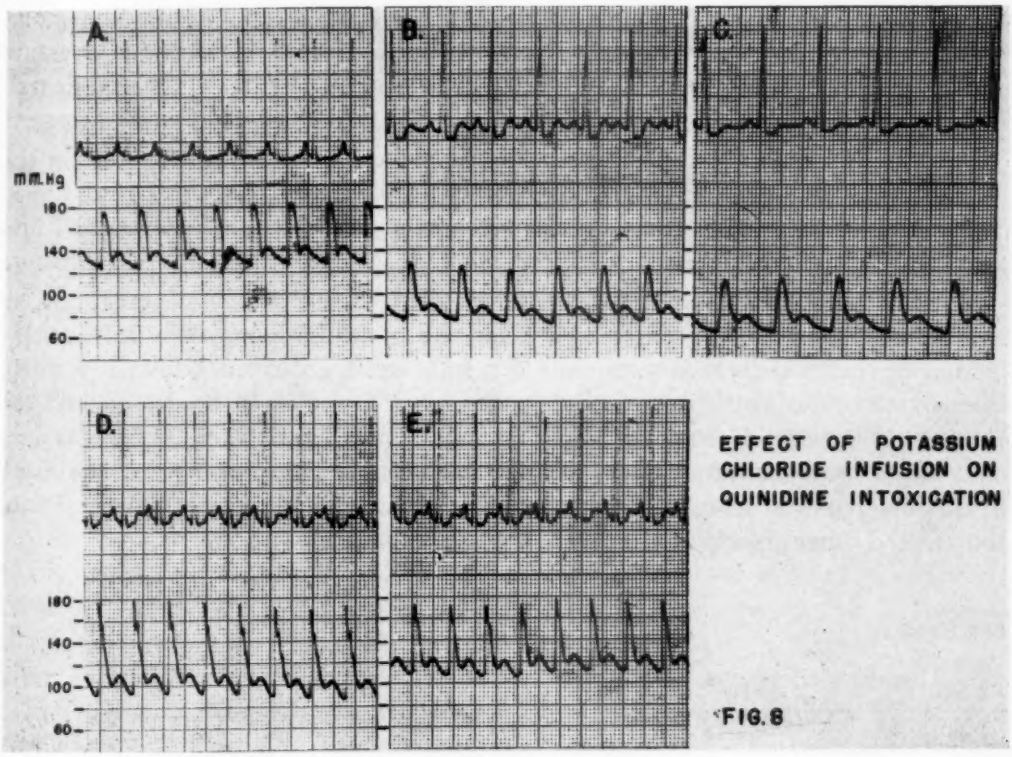

Fig. 8.—Effect of quinidine and potassium chloride on the electrocardiogram (Lead II) and blood pressure. *A*, Control. Pulse rate 170/min., QRS 0.04 sec., blood pressure 180/124 mm. Hg, plasma potassium 3.2 mEq./L., pH 7.40. *B*, Immediately after quinidine. Pulse rate 136/min., QRS 0.07 sec., blood pressure 124/72 mm. Hg, plasma potassium 2.8 mEq./L., pH 7.32, plasma quinidine 20 mg./L. *C*, Ten minutes after quinidine. There was further slowing of pulse and drop in blood pressure. *D*, Five minutes after 15 mEq. of potassium chloride. Pulse rate 182/min., QRS 0.05 sec., blood pressure 176/92 mm. Hg. (Immediately after infusion of potassium chloride, plasma potassium was 6.5 mEq. /L.) *E*, sixty minutes after quinidine (40 minutes after potassium chloride). Pulse rate 182/min., QRS 0.04 sec., blood pressure 174/108 mm. Hg, plasma potassium 3.7 mEq./L., pH 7.41, plasma quinidine 7 mg./L.

After injection of quinidine, the P wave widened from an average control of 0.04 to 0.06 second and became somewhat taller initially. It decreased in amplitude gradually. One dog in Group 1 (quinidine) and 2 dogs in Group 6 (quinidine–molar sodium lactate, repeated doses), developed nodal rhythm. In each instance, the nodal rhythm was transient, lasting from 1 to 10 minutes, and was replaced by sinus rhythm spontaneously. The nodal rhythm was not accompanied by

any change in systemic blood pressure. After quinidine, the P-R interval and QRS duration increased and the S-T segment showed depression. In the first five groups, the P-R interval increased from the control range of 0.08 to 0.10 second to 0.12 to 0.16 second. The QRS duration widened from the control range of 0.04 to 0.05 second to 0.06 to 0.09 second.

In Group 6 (quinidine–molar sodium lactate, repeated doses), the QRS duration widened to 0.10 to 0.13 second after the initial injection of quinidine. Further increase occurred after additional quinidine.

Approximately 5 minutes after injection of molar sodium lactate, there was a decrease in the P-R interval and duration of QRS in Group 2 (quinidine–molar sodium lactate), concomitant with the increase in pulse rate and blood pressure (Fig. 6). However, in Group 6 (quinidine–molar sodium lactate, repeated doses), 2 dogs showed a decrease in QRS duration without any increase in blood pressure.

Potassium chloride in the doses described had no significant effect on the P-R interval and the QRS duration, except in 2 dogs in Group 4 (quinidine–potassium chloride). These dogs demonstrated a decrease in P-R interval and duration of QRS concomitant with the increased pulse rate and blood pressure (Fig. 8).

A prominent U wave appeared after the administration of quinidine. Injection of molar sodium lactate caused a further accentuated U wave (Fig. 6), whereas the administration of potassium chloride abolished or diminished the U wave. U waves did not occur in the dogs in Group 5 which received potassium chloride prior to quinidine. The U wave remained more prominent in Group 2 (quinidine–molar sodium lactate) and Group 3 (molar sodium lactate–quinidine) than in the other groups at the end of the period of observation.

DISCUSSION

Although the exact mechanism of the pharmacologic effect of quinidine is not clearly understood, quinidine is known to cause pronounced changes in carbohydrate metabolism.[9,10] During the administration of quinidine to human subjects, Furman and Howard[9] noted impaired glucose tolerance curves. According to Uyeki and his associates,[10] quinidine sulfate inhibits the oxidation of glucose, pyruvate, and certain other substrates of rat heart slices, possibly by inhibiting transphosphorylating enzymes. Under physiologic conditions the fuel of cardiac muscle consists mainly of glucose, lactate, pyruvate, and nonesterified fatty acid.[11-13] Conceivably, therefore, interference of carbohydrate metabolism may cause an alteration in the production of myocardial energy.

The intravenous administration of quinidine is followed by alteration in electrolytes, although reports of the related findings have not been consistent. Wasserman and his co-workers[4] found no changes in electrolytes after the administration of quinidine. However, Bellet and his colleagues[5] demonstrated significant decreases in plasma potassium, sodium, and magnesium. At the time of quinidine intoxication, an increase in serum potassium from 5.0 to 6.2 mEq. per liter was found in 1 of the 2 patients reported by Bailey.[6]

In the present report, significant decreases in plasma potassium occurred immediately after administration of quinidine and persisted during the 60-minute period of observation. There was no significant change in the concentration of plasma sodium. Since this change in plasma potassium occurred within 10 minutes, it is not conceivable that all of the decrease in potassium was through renal excretion. Normal saline solution given in volumes similar to the quinidine solution did not alter the level of plasma potassium. Therefore, the decrease in plasma potassium after injection of quinidine cannot be explained on the basis of hemodilution. Decreased plasma potassium has been observed in experimental animals with respiratory alkalosis.[14,15] It has been suggested that these changes in potassium represent alterations in the extracellular-intracellular ratio rather than alteration in the total body content of potassium. However, the decrease in plasma potassium after injection of quinidine cannot be explained by respiratory alkalosis, since the change also occurred in dogs with normal and relatively low arterial blood pH. Since the administration of quinidine results in an increase in the potassium in the myocardium,[7] the decrease in plasma potassium after the injection of quinidine may be explained by the shift of potassium to cells. Holland[16] suggested that quinidine depresses the outward flux of the potassium ion by blocking the action of intracellularly released acetylcholine. Armitage[17] stated that when quinidine was perfused through the intact heart, or when it acted on atrial muscle, it caused the cell membrane to become less permeable to potassium ions. Peripheral vasodilatation has been observed after the administration of quinidine.[18] The drop in the diastolic pressure and the resultant increase in pulse pressure at the initial stage of injection of quinidine suggest its profound effect on the autonomic nervous system.

Previous investigators[1-6] have reported that molar sodium lactate is beneficial in the treatment of quinidine intoxication. This benefit was related to improvement of blood pressure, increase in the pulse rate, and narrowing of P-R interval and QRS duration after infusion of molar sodium lactate.

Our studies in dogs showed that molar sodium lactate was beneficial in the treatment of moderate quinidine intoxication, but it did not have significant value in the treatment of severe quinidine intoxication and, when given prophylactically, failed to prevent the drop in blood pressure. Moreover, 3 dogs developed a significant arrhythmia after injections of molar sodium lactate. A similar finding was reported by Murray and Boyer.[19] In 12 patients who received molar sodium lactate for the treatment of heart block and bradycardia, there was an increased frequency of ectopic contractions in 7 patients.

The mechanisms of the effect of molar sodium lactate have been variously explained as being due to a decrease in plasma potassium, a shift of the blood pH to the alkalotic side, a decrease in concentration of plasma quinidine, or a direct effect of the lactate and an increase in blood pressure with a resultant improvement in renal function and tissue blood flow.[4,5] Holland,[16] using the atria of young rabbits, showed that the effect of quinidine could be enhanced by elevating the level of potassium of the medium twofold and could be blocked completely by lowering the potassium to one sixteenth of the normal amount. The synergistic effect of quinidine and potassium could not be demonstrated under the conditions

of present study. Furthermore, the effect of quinidine in those dogs which received potassium chloride prior to the administration of quinidine was not greater than in the other groups.

Although the pH increases after molar sodium lactate, it is doubtful whether this is significant in the treatment of quinidine intoxication. The pH, although definitely decreased after administration of quinidine, remained well within normal limits in most of the dogs. In some of the dogs, the blood pH was on the alkalotic side even after injection of quinidine.

A direct beneficial effect of lactate on the myocardium has been suggested since lactate has been known to be utilized by the myocardium.[20-22] Bogue and co-workers[22] found that the isolated canine heart removed more lactate from the blood than any other substance. During studies on man, Bing and his associates[23] observed that a rise in concentration of arterial blood lactate led to an increased extraction of lactate by the myocardium.

A decrease in the concentration of quinidine after infusion of molar sodium lactate was attributed, by Bellet and associates,[5] to the result of the expansion of the extracellular space.

However, the rapid decrease in the levels of plasma quinidine after intravenous administration of quinidine appears to be little altered from the control in any instance, except when molar sodium lactate had been given prophylactically. In Group 6 (quinidine–molar sodium lactate, repeated doses), the decrease in the level of plasma quinidine after infusion of molar sodium lactate is rapid (Fig. 2). The decrease cannot be directly ascribed to the molar sodium lactate, since equally rapid decrease in concentration of plasma quinidine occurs when no molar sodium lactate has been given.

Usually when quinidine is given to man orally, only one half to one third of the peak concentration of plasma remains 12 hours after the last dose.[24,25] However, it has been noted that patients with heart failure generally have a slower disappearance rate of quinidine from plasma as compared to controls.[25] We have observed a patient with renal impairment in whom the concentration of plasma quinidine was identical to the peak level 12 hours after the last dose.

There was no significant decrease in the concentration of plasma quinidine after the infusion of molar sodium lactate in the cases reported by Wasserman and his associates,[3] but there was a considerable drop in the concentration of plasma quinidine after infusion of molar sodium lactate in the cases reported by Bailey.[6]

It is difficult to relate the change in the level of plasma quinidine to any beneficial effect of molar sodium lactate on quinidine toxicity. Since molar sodium lactate lowers the plasma potassium and corrects acidosis, it may be recommended for those patients who have quinidine intoxication concurrently with hyperpotassemia and acidosis. However, the effects of quinidine on the blood pH and electrolytes have not been sufficiently investigated in man. Whether molar sodium lactate has any real place in the treatment of quinidine intoxication is not certain and remains to be determined.

SUMMARY

1. Thirty-six dogs which weighed 7 to 13 kilograms were studied for the changes in plasma potassium, sodium, arterial blood pH, electrocardiogram, and arterial blood pressure after intravenous administration of quinidine. The effects of molar sodium lactate and potassium chloride given prior to or after the administration of quinidine were determined.

2. There was a definite decrease in the concentration of plasma potassium and in arterial blood pH after the intravenous administration of quinidine. The mean decrease in plasma potassium was 0.6 and 0.9 mEq. per liter for moderate and severe quinidine intoxication, respectively. The mean decrease in arterial blood pH ranged from 0.04 to 0.09. No significant change in plasma sodium was noted.

3. When quinidine was given initially and followed by molar sodium lactate, there was a further decrease in plasma potassium (mean decrease of 0.4 mEq. per liter), a moderate increase in blood pressure and pulse rate, narrowing of the P-R interval and QRS duration, and appearance of a prominent U wave.

4. When given prophylactically, molar sodium lactate failed to prevent the hypotensive effect of quinidine, and had no significant beneficial effect on severe quinidine intoxication.

5. When quinidine was followed by potassium chloride, 2 out of 5 dogs developed a significant increase in pulse rate and blood pressure. Similar doses of potassium chloride given prior to the administration of quinidine did not enhance the effect of quinidine.

6. The possible mechanisms of action of molar sodium lactate are discussed.

7. Whether molar sodium lactate has any significant value in the treatment of quinidine intoxication remains to be determined.

The guidance and encouragement of Dr. Leonard Scherlis are gratefully acknowledged. I am indebted to Miss Evelyn Rice for technical assistance.

REFERENCES

1. Bellet, S., Hamden, G., and Somlyo, A.: Reversal of Cardiotoxic Effect of Quinidine by Molar Sodium Lactate, Clin. Res. **6**:226, 1958.
2. Wasserman, F., Brodsky, L., Kathe, J. H., Rodensky, P. L., Dick, M. M., and Denton, P. S.: Method for the Treatment of Quinidine and Procaine Amidine Intoxication: A Clinical and Experimental Study, Clin. Res. **6**:227, 1958.
3. Wasserman, F., Brodsky, L., Dick, M. M., Kathe, J. H., and Rodensky, P. L.: Successful Treatment of Quinidine and Procaine Amide Intoxication: Report of Three Cases, New England J. Med. **259**:797, 1958.
4. Wasserman, F., Brodsky, L., Kathe, J. H., Rodensky, P. L., Dick, M. M., and Denton, P. S.: The Effect of Molar Sodium Lactate in Quinidine Intoxication: An Experimental Study, Am. J. Cardiol. **3**:294, 1959.
5. Bellet, S., Hamden, G., Somlyo, A., and Lara, R.: The Reversal of the Cardiotoxic Effects of Quinidine by Molar Sodium Lactate: An Experimental Study, Am. J. M. Sc. **237**:165, 1959.
6. Bailey, D. J., Jr.: Cardiotoxic Effects of Quinidine and Their Treatment, A.M.A. Arch. Int. Med. **105**:13, 1960.
7. Gertler, M. M., Kream, J., Hylin, J. W., Robinson, H., and Neidle, E. G.: Effect of Digoxin and Quinidine on Intracellular Electrolytes of the Rabbit Heart, Proc. Soc. Exper. Biol. & Med. **92**:629, 1956.
8. Brodie, B., and Udenfriend, S.: The Estimation of Quinine in Human Plasma, With a Note on the Estimation of Quinidine, J. Pharmacol. & Exper. Therap. **78**:154, 1943.

9. Furman, R. H., and Howard, R. P.: Metabolic Effect of Quinidine: Evidence Suggesting Impairment of Glucose Utilization, Am. J. Med. **19**:140, 1955.
10. Uyeki, E. M., Geiling, E. M. R., and Dubois, K. P.: Studies on the Effects of Quinidine on the Intermediary Carbohydrate Metabolism, Arch. internat. pharmacodyn. **97**:191 1954.
11. Bing, R. J.: Myocardial Metabolism, Circulation **12**:635, 1955.
12. Gordon, R. S., and Cherkes, A.: Unesterified Fatty Acid in Human Blood Plasma, J. Clin. Invest. **35**:206, 1956.
13. Olson, R. E.: Myocardial Metabolism in Congestive Heart Failure, J. Chron. Dis. **9**:442, 1959.
14. Abrams, W. B., and Lewis, D. W.: The Effect of Acidosis and Alkalosis on the Plasma Potassium Concentration and the Electrocardiogram of Normal and Potassium Depleted Dogs, Am. J. M. Sc. **222**:506, 1951.
15. Scribner, B. H., and Burnell, J. M.: The Effect of Respiratory Alterations of pH on the Internal Equilibrium of Potassium, J. Clin. Invest. **34**:919, 1955.
16. Holland, W. C.: Possible Mechanism of Action of Quinidine, Am. J. Physiol. **190**:492, 1957.
17. Armitage, A. K.: The Influence of Potassium Concentration of the Action of Quinidine and of Some Antimalarial Substances on Cardiac Muscle, Brit. J. Pharmacol. **12**:75, 1957.
18. Ferrer, M. I., Harvey, R. M., Werkö, L., Dresdale, D. T., Cournand, A., and Richards, D. W., Jr.: Some Effects of Quinidine Sulfate on the Heart and Circulation in Man, Am. Heart J. **36**:816, 1948.
19. Murray, J. F., and Boyer, S. H.: Ventricular Arrhythmia After Intravenous Sodium Lactate in Heart Block, Circulation **15**:547, 1957.
20. Himwich, H. E., Koskoff, Y. D., and Nahum, L. H.: Changes in Lactic Acid and Glucose in the Blood on Its Passage Through Organs, Am. J. Physiol. **85**:379, 1928.
21. Evans, C. A. L.: The Metabolism of Cardiac Muscle. *In* Recent Advances in Physiology, ed. 6, Philadelphia, 1939, The Blakiston Company, p. 490.
22. Bogue, J. Y., Evance, C. L., Grande, F., and Hsu, F. Y.: Effect of Adrenaline and of Increased Work on Carbohydrate Metabolism of Mammalian Heart, Quart. J. Exper. Physiol. **25**:213, 1935.
23. Bing, R. J., Siegel, A., Vitale, A., Balboni, F., Sparks, E., Taeschler, M., Klapper, M., and Edwards, S.: Metabolic Studies on Human Heart in Vivo. I. Studies on Carbohydrate Metabolism of the Human Heart, Am. J. Med. **15**:284, 1953.
24. Sokolow, M., and Edgar, A. L.: Blood Quinidine Concentration as Guide in the Treatment of Cardiac Arrhythmia, Circulation **1**:576, 1950.
25. Brown, M. G., Holzman, D., and Greelman, E. W.: Serum Quinidine Concentration in Congestive Heart Failure, Am. J. M. Sc. **225**:129, 1953.

Studies on the Influence of Anabolic Steroids on Experimental Atheroma: 17-Alpha-Ethyl-19-Nortestosterone (Nilevar)

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In previous experiments it has been shown that the anabolic compounds with weak androgenic activity, 19-nortestosterone phenyl propionate (Durabolin), and androstane 17-beta-ol-3 one (Anabolex) appear to reduce the incidence of coronary arterial atheroma in the cholesterol-fed cockerel (Campbell and associates[1,2]). The effect on atheroma of another 19-nortestosterone derivative, 17-alpha-ethyl-19-nortestosterone (Nilevar), also having strongly anabolic properties and relatively mild androgenicity, is reported in this paper, together with an account of its effect on the plasma lipids. These results are compared with our findings in the previous experiments.

MATERIAL AND METHODS

The experimental plan, based on that of Pick and associates,[4] was the same as that used in other experiments of this series. Fifty-two Golden Legbar × Light Sussex cockerels, 8 weeks old at the start of the experiment, were used. They were kept in individual cages and fed ad libitum. The atherogenic diet consisted of commercial chick mash supplemented with 2 per cent cholesterol and 5 per cent cottonseed oil. The birds were grouped as follows: *Group A:* 4 birds, fed on commercial mash alone for 8 weeks; *Group B:* 12 birds, fed on atherogenic diet for 8 weeks; *Group C:* 12 birds, fed on atherogenic diet for 8 weeks and, in addition, receiving during the latter 3 weeks, 1 mg. of 17 alpha-ethyl-19-nortestosterone; *Group D:* 12 birds, fed as were those in Group C except that the dosage of 17 alpha-ethyl-19-nortestosterone was 5 mg. daily; *Group E:* 12 birds, fed on commercial mash for 8 weeks, and receiving during the latter 3 weeks 1 mg. of 17 alpha-ethyl-19-nortestosterone daily by intramuscular injection.

The birds were weighed, and their daily intake of food was estimated at intervals. Blood was taken from an alar vein into heparinized tubes at the beginning of the experiment, and at the end of the fifth and eighth weeks. Plasma cholesterol was estimated by a modified Sperry-Schoenheimer technique,[5] and plasma phospholipids by the method of King and Wooton.[3]

Each bird was killed by cervical dislocation, and the aorta and brachiocephalic arteries were examined macroscopically for atheroma. The severity of involvement was graded as follows:

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slight atheroma implied focal lesions up to about 2 mm. in diameter, of white or pale cream color, accompanied by minimal gross thickening of the intima; *moderate* lesions consisted of plaques up to 5 mm. in diameter, cream or ivory-yellow in color, sometimes with distinct intimal thickening and longitudinal ("tree-trunk") ridging; in *severe* cases larger plaques of cream to yellow color merged into diffuse atheroma. There was distinct thickening, ridging, and sometimes distortion of the wall.

The heart was fixed in 10 per cent formol-saline, and three transverse slices were taken through the ventricular zone, excluding the apex. One frozen section was prepared from each slice and stained with Sudan IV and hemalum. The groups were coded and read in single-blind fashion when the microscopic count of coronary arteries was carried out. Any sudanophilic intimal thickening or plaque formation was regarded as indicative of atheroma. Slight sudanophilia alone without structural changes was disregarded. The incidence of atheroma was expressed as a percentage for each group.

The statistical method employed was the analysis of variance and covariance.

RESULTS

Body Weight and Food Intake.—Satisfactory assessment of those findings was difficult because of the lack of comparable figures for the eighth week in Groups A and E. Treated groups appeared to gain weight at about the same rate, although the intake of food was somewhat lower from the sixth week in the groups receiving the atherogenic diet and anabolic drug.

Plasma Cholesterol, Phospholipid, and Cholesterol-Phospholipid (C/P) Ratio.—Group mean values are presented in Table I. There was no statistical difference between the results obtained from the treated and untreated cholesterol-fed birds (Groups B, C, and D) at the fifth or eighth week.

TABLE I. MEAN VALUES FOR PLASMA CHOLESTEROL (C) (mg./100 ml.), PHOSPHOLIPID (P) (mg./100 ml.), AND CHOLESTEROL/PHOSPHOLIPID RATIO (C/P)

GROUP	FIFTH WEEK			EIGHTH WEEK		
	C	P	C/P	C	P	C/P
A	136	8.9	15.4	138	9.1	15.4
B	1,117	16.6	67.3	1,280	17.8	72.1
C	1,167	19.0	61.4	1,305	17.8	73.7
D	977	19.6	49.8	1,506	21.28	71.0
E	131	9.6	14.0	141	8.8	16.2

TABLE II. THE SEVERITY OF AORTIC LESIONS

GROUP	GRADE OF SEVERITY			
	ABSENT	SLIGHT	MODERATE	SEVERE
A	4	0	0	0
B	3	1	4	4
C	1	0	7	4
D	1	2	4	5
E	6	5	1	0

Atheroma.—The incidence of aortic and coronary atheroma is shown in Tables II and III. The incidence of coronary lesions was less in both treated groups than in the controls on the high-cholesterol and fat diet, but only with the 1-mg. dose was this reduction statistically significant. There was little difference in the severity of aortic lesions among the three groups receiving cholesterol.

Testicular Size and Secondary Sex Characters.—Group means for testicular and comb size are shown in Table IV. There was little difference in testicular size between the groups, although it tended to be less in cockerels receiving both 17-alpha-ethyl-19-nortestosterone and the atherogenic diet. Comb development, on the other hand, appeared to be enhanced in the treated birds.

TABLE III. THE INCIDENCE OF CORONARY ARTERY LESIONS

GROUP	NUMBER OF BIRDS AFFECTED	NUMBER OF VESSELS COUNTED	PER CENT OF VESSELS AFFECTED
B	12	544	23.7
C	12	423	9.1
D	12	585	17.6

TABLE IV. TESTICULAR AND COMB SIZE—GROUP MEANS (CM.)

GROUP	TESTES	COMB
A	$2.9 \times 1.6 = 4.64$	$9.6 \times 4.8 = 46.08$
B	$3.1 \times 1.5 = 4.65$	$9.2 \times 4.6 = 42.3$
C	$2.6 \times 1.3 = 3.38$	$9.8 \times 4.8 = 47.0$
D	$2.9 \times 1.5 = 4.35$	$10.0 \times 5.4 = 54.0$
E	$3.4 \times 1.7 = 5.78$	$9.8 \times 5.0 = 49.0$

DISCUSSION

These results indicate that 17-alpha-ethyl-19-nortestosterone may reduce the incidence of coronary atheroma in the cholesterol-fed cockerel, and that it does so without significant alteration in plasma cholesterol and levels of phospholipid, or in the C/P ratio. The effects are similar to those obtained with 19-nortestosterone phenyl propionate and androstane 17-beta-ol-3 one, which for the purpose of comparison are set out in Table V. The only substance in this group to have any apparent action on the plasma lipids was 19-nortestosterone phenyl propionate, which caused a reduction both in the levels of cholesterol and in the C/P ratios when given in 1-mg. dosage. There was suggestive evidence at this dosage that it also reduced the severity of aortic atheroma, whereas 17-alpha-ethyl-19-nortestosterone and androstane 17-beta-ol-3 one in approximately equivalent dosage had no significant influence on it.

The mode of action of these steroids on experimental coronary atheroma in the cockerel is not clear. The fact that a similar result has been obtained with three compounds, each with the common property of anabolic or protein-sparing

action, suggests that this might be the means by which they reduce the incidence of coronary atheroma. There is some evidence from one of our experiments[1] to suggest that they prevent the deposition of lipid on the vessel wall rather than remove material previously deposited. If so, it may be that even in the presence of hypercholesterolemia and hyperphospholipemia, atheromatous change in the vessel wall may be prevented.

The recent observation by Stamler and associates[6] that, in the cockerel, a diet supplemented with protein led to a reduced incidence of coronary lesions may be indirect evidence that the protein-sparing activity of these steroids is related to their action against atheroma.

TABLE V. COMPARISON OF THE EFFECT ON EXPERIMENTALLY INDUCED ATHEROMA IN THE COCKEREL OF THE THREE ANABOLIC SUBSTANCES*

		INCIDENCE OF CORONARY ATHEROMA	
ANABOLIC AGENT	DOSE (MG.)	TREATED BIRDS (%)	CONTROL BIRDS (%)
19-Nortestosterone phenyl propionate	1	18.6	37.3
	5	16.2	
Androstane 17-beta-ol-3 one	5	10.3	22.2
	25	10.7	
17-Alpha-ethyl-19-nortestosterone	1	9.1	23.7
	5	17.6	

*The three substances are: 19-nortestosterone phenyl propionate (Durabolin); androstane 17-beta-ol-3 one (Anabolex); and 17-alpha-ethyl-19-nortestosterone (Nilevar).

As yet it is not possible to explain why the coronary vessels should be selectively aided when there was little change in aortic atheroma, and when levels of plasma lipid were not reduced. Nor can we state the significance, if any, of these findings in relation to human atherosclerosis, but they raise the possibility that assessment of response to therapy of atherosclerosis based on levels of blood lipid may be inaccurate.

SUMMARY

The effect of 17-alpha-ethyl-19 nortestosterone (Nilevar) on experimentally induced atheroma and the plasma lipids in the cockerel is described. The incidence of coronary arterial lesions was lower in the treated birds than in controls, and with the 1-mg. dose this reduction was statistically significant. There were no statistical differences in the plasma cholesterol or phospholipid levels or in the cholesterol/phospholipid ratio between the treated birds and the cholesterol-fed controls.

The results are compared with those obtained in similar experiments in which were used the anabolic substances 19-nortestosterone phenyl propionate and androstane 17-beta-ol-3 one.

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REFERENCES

1. Campbell, R. S. F., Lawrie, T. D. V., Maclaurin, J. C., and Pirrie, R.: The Effect of 19-Nor-androstanolone on Experimentally Induced Atheroma in Cockerels, Circulation Res. **8**:78, 1960.
2. Campbell, R. S. F., Lawrie, T. D. V., McAlpine, S. G., Pirrie, R., and Rifkind, B.: Studies on the Influence of Anabolic Steroids on Experimental Atheroma: Androstanolone, J. Endocrinol. **20**:246, 1960.
3. King, E. J., and Wooton, I. D. P.: Microanalysis in Medical Biochemistry, London, 1956, J. & A. Churchill, Ltd.
4. Pick, R., Stamler, J., Rodbard, S., and Katz, L. N.: Estrogen-Induced Regression of Coronary Atherosclerosis in Cholesterol-Fed Chicks, Circulation **6**:858, 1952.
5. Schoenheimer, R., and Sperry, W. M.: Micromethod for Determination of Free and Combined Cholesterol, J. Biol. Chem. **106**:745, 1934.
6. Stamler, J., Pick, R., and Katz, L. N.: Effects of Dietary Protein and Carbohydrate Level on Cholesterolemia and Atherogenesis in Cockerels on a High-fat, High-Cholesterol Mash, Circulation Res. **6**:447, 1958.

Case Reports

Unusual Left Atrial Enlargement With Patent Ductus Arteriosus

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INTRODUCTION

In 1806, Corvisart[1] was aware that left atrial enlargement occurred when the circulation was impeded by cartilaginous or bony hardening of the left atrioventricular valve. Rigler,[2] in 1929, firmly established the use of the barium-filled esophagus for the radiologic detection of left atrial enlargement in patients with mitral stenosis. Although it is well documented that the left atrium might enlarge in conditions other than mitral valve disease,[3-11] the observation is still not commonly appreciated. The point was recently emphasized to us when a 37-year-old woman with clinical and physiologic features of patent ductus arteriosus (proved by surgery) presented with such striking enlargement of the left atrium that several observers entertained the diagnosis of coexisting mitral stenosis. These initial observations, together with equally striking postoperative regression, were considered sufficiently impressive to justify a detailed report.

CASE REPORT

History.—The patient, a 37-year-old white woman, was admitted to Georgetown University Hospital for cardiac evaluation. She was born of a normal pregnancy. When she was 5 years old, a murmur was detected. There was no history of rheumatic fever or its stigmata. Growth and development were normal. Easy fatigability was the only symptom during childhood and adolescence, during which time periodic school examinations confirmed the murmur. She had been pregnant at the age of 26, 27, 29, and 31 years. The first of these pregnancies had been uneventful, but congestive cardiac failure of moderate severity occurred with the last three pregnancies. During the 6 years prior to admission, fatigability, mild diurnal pedal edema, and occasional nocturnal dyspnea appeared. Two weeks prior to admission, irregular, forceful palpitation developed, associated with increasing shortness of breath.

Physical Examination.—The patient was a well-developed woman in mild respiratory distress. Significant physical findings were confined to the cardiovascular system. Blood pressure in both

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arms was 130/50 mm. Hg, and in both legs it was 160/50 mm. Hg. The cardiac rhythm was basically regular, with frequent premature contractions, many of which caused bigeminal rhythm. The arterial pulses were symmetrical and sharp-rising, with a Corrigan quality. The jugular venous pulse was moderately elevated, and the liver was two fingerbreadths below the costal margin, but edema was not present. The lungs were clear to percussion and auscultation. A rather vigorous left ventricular thrust formed the apex in the fifth intercostal space between the mid-clavicular and anterior axillary lines, and a moderate parasternal lift was felt over the right ventricle. In

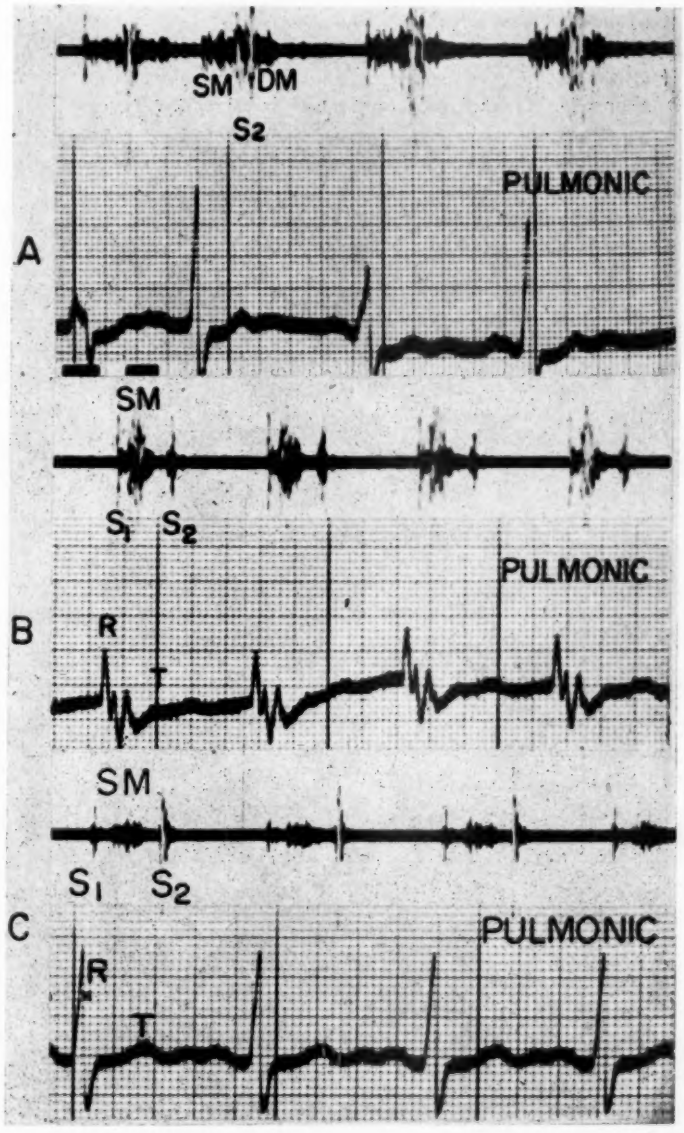

Fig. 1.—*A*, Preoperative phonocardiogram recorded in the pulmonary area, illustrating a murmur beginning in early systole (*SM*), rising in crescendo in the latter part of systole, and going through the second heart sound (S_2) into early diastole (*DM*). *B*, Phonocardiogram recorded in the pulmonary area immediately postoperatively, illustrating a short ejection type of systolic murmur which is believed to be due to flow across a normal pulmonic valve into a dilated pulmonary artery (S_1: first heart sound). *C*, Phonocardiogram recorded in the pulmonary area 1 year postoperatively, illustrating the decreased intensity of the murmur across the pulmonic valve.

the second left intercostal space a long, systolic thrill and a palpable second heart sound were appreciated. Auscultation revealed a normal first heart sound at the apex and left sternal edge. At the pulmonary area, a widely radiating Grade 4, harsh, machinery type of murmur was heard. It occupied all of systole and continued beyond the second heart sound into early diastole, clearly ending before the next cardiac cycle (Fig. 1,*A*). The second sound in the pulmonic area and subjacent left sternal edge was single and moderately accentuated. There was a third heart sound at the cardiac apex, followed by a short, variable mid-diastolic murmur. Postoperatively the machinery type of murmur and the apical mid-diastolic murmur disappeared. In the pulmonary area there remained a short ejection systolic murmur (Fig. 1,*B*), which markedly decreased in intensity during the following year (Fig. 1,*C*).

Laboratory Data.—

Peripheral blood: The hemoglobin was 14 Gm./100 c.c. Hematocrit was 43 per cent. The corrected sedimentation rate was 16; white blood count 7,200, lymphocytes 24 per cent, monocytes 2 per cent, mature polymorphonuclear leukocytes 67 per cent, band forms 7 per cent.

Urinalysis: Specific gravity of the urine was 1.025; pH 6, albumin negative; sugar negative, microscopic negative.

Blood urea nitrogen: 18 mg. per 100 ml.

Fasting blood sugar: 106 mg. per 100 ml.

Stool guaiac: negative.

X-ray examination (Fig. 2): Radiologic studies revealed biventricular enlargement and increased pulmonary blood flow. The pulmonary artery segment was 2+ enlarged. In the postero-anterior projection, a left atrial double density was seen, and a barium swallow in the right anterior oblique view defined discrete esophageal displacement caused by marked enlargement of the left atrium. No calcium could be seen in the region of the mitral valve.

TABLE I. PHYSIOLOGIC DATA

CATHETER POSITION	OXYGEN CONTENT (VOL. %)	PRESSURES (MM./HG)
F.A.	19.8	130/40
SVC	14	—
IVC	15.9	—
R.A.	14.5	6 (Mean)
R.A.	14.0	—
R.V.	13.9	42/3
R.V.	14.1	—
P.A. (Main)	18.8	42/18 26 (Mean)
P.A. (Left)	18.7	—

Oxygen capacity: 20.5 volumes per cent
Arterial saturation: 96 per cent
Systemic flow: 2.8 liters
Pulmonary flow: 15 liters
Pulmonary/Systemic flow ratio: 5/1
Total pulmonary resistance: 140 dynes sec. cm.$^{-5}$

Electrocardiograms (Fig. 3): The basic rhythm was normal sinus. Frequent premature ventricular contractions occurred often, causing bigeminal rhythm. There were episodes of sinus arrest followed by nodal escape beats. Left atrial enlargement was diagnosed on the basis of the contour and duration of the P wave. The electrical axis was horizontal, with left ventricular hypertrophy and strain and a parietal type of left ventricular conduction defect.

Cardiac catheterization: The data, summarized in Table I, were interpreted as indicating a large left-to-right shunt into the pulmonary artery through a patent ductus arteriosus. The moderate elevation in pulmonary arterial pressure appeared to be due to the magnitude of pulmonary blood flow with a low total pulmonary vascular resistance.

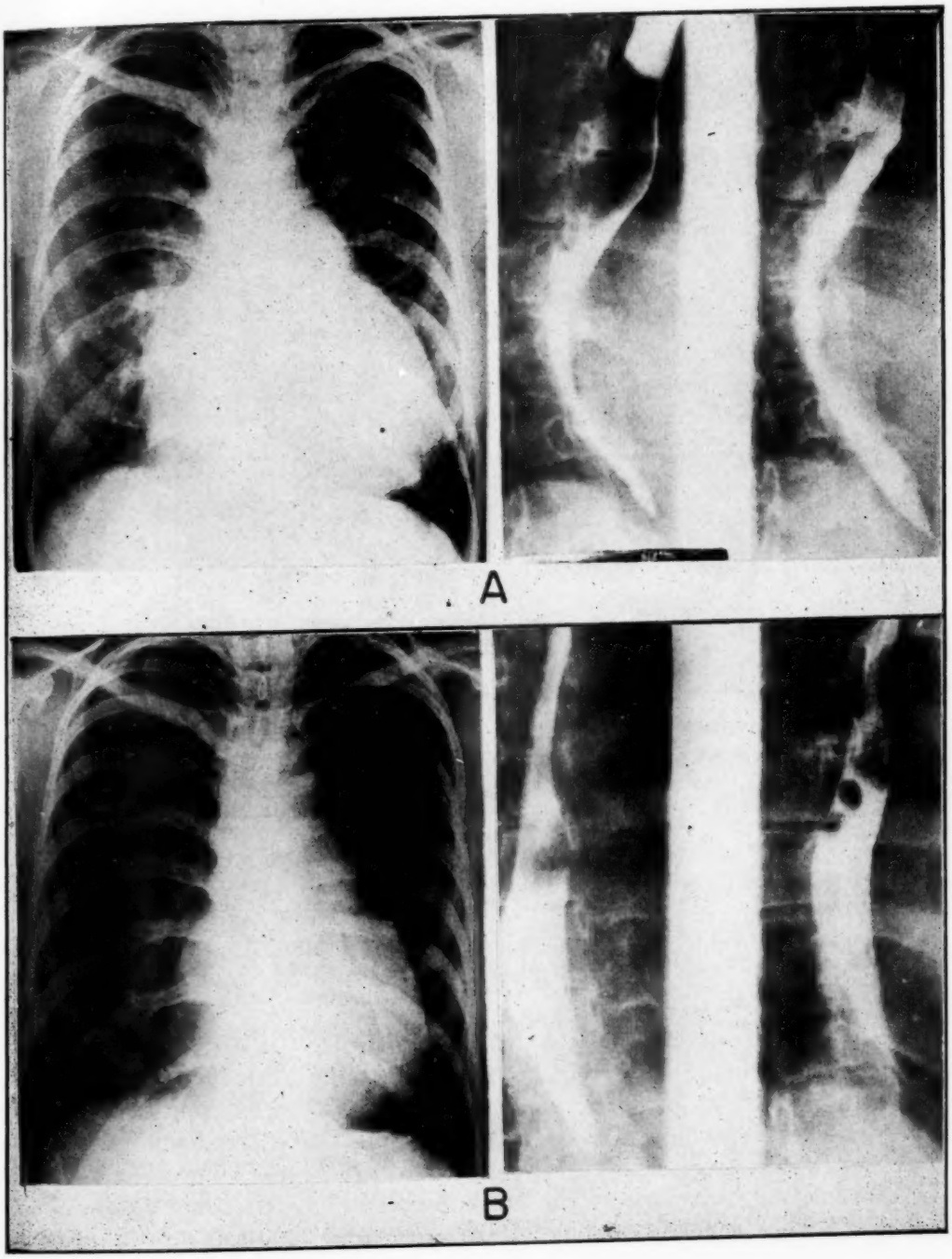

Fig. 2.—*A*, Preoperative chest x-ray films. There is radiologic evidence of biventricular enlargement, dilatation of the pulmonary artery, and increased pulmonary blood flow. The right oblique views (slightly different degrees of rotation) illustrate unusual enlargement of the left atrium causing high, discrete displacement of the barium-filled esophagus. *B*, X-ray films recorded 1 year postoperatively. The pulmonary blood flow appears normal. The sizes of the pulmonary artery and the ventricles have materially decreased. The right anterior oblique views illustrate striking regression of the left atrial enlargement.

Operative Summary.—The lesion was approached through a left thoracotomy. The patent ductus arteriosus was dissected free and was found to be short in length and about the thickness of the surgeon's thumb. It was cross clamped, divided, and sutured. No other abnormalities were described in the operative note.

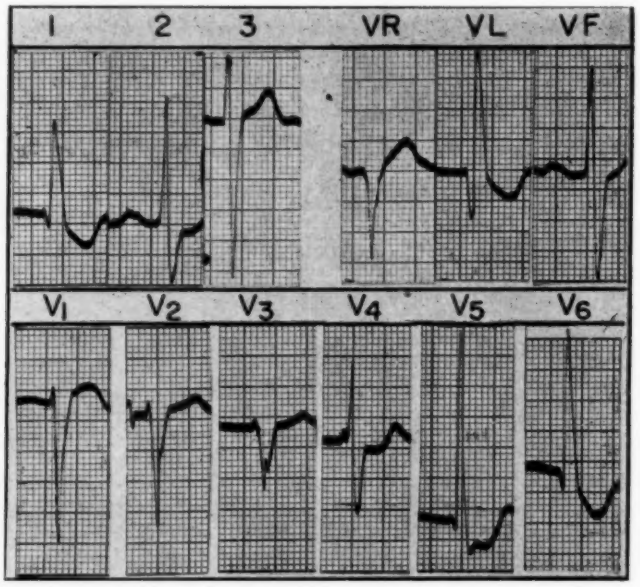

Fig. 3.—Preoperative electrocardiogram. Note the broad, notched P wave in Lead II.

COMMENTS

Enlargement of the left atrium is a cardinal feature of rheumatic mitral valve disease.[12] It is now an established, although poorly recognized, observation that this chamber may increase in size under a variety of other stimuli,[3,7-11] such as coarctation of the aorta, thyrotoxicosis, prolonged atrial fibrillation, or flutter, complete heart block, constrictive pericarditis, and congenital heart disease with left-to-right shunts.

Radiologic assessment of left atrial enlargement, with autopsy quantitation of left atrial volume,[6] has demonstrated a detectable increase in the size of the left atrium in cases of aortic stenosis, systemic hypertension, and coronary artery disease, especially with co-existing myocardial failure. Although enlargement was not so great as with mitral valve disease, it was found that left atrial volume may be twice normal in the groups with hypertension and coronary artery disease. Congenital lesions (other than patent ductus arteriosus) in which the left atrium is the recipient of a central shunt might also cause this chamber to enlarge. The most common of these is ventricular septal defect,[3,9,10] although an increase in atrial size has been described in cases of coronary arteriovenous fistula as well.[4,5] Using electrocardiographic criteria, Macruz and co-workers[13] diagnosed left atrial enlargement in 70 per cent of the congenital cases with "left atrial preponderance," including ventricular septal defect, patent ductus arteriosus, coarctation of the aorta, and aortic stenosis. It must clearly be stated

that in any such interpretation of the esophagram, care must be taken to distinguish high discrete esophageal displacement of the enlarged left atrium from diffuse retrodisplacement, especially that associated with left ventricular cardiomegaly.[8,11]

In cases of patent ductus arteriosus, the combination of fullness of the left atrium, an apical diastolic murmur, bifid P waves, and increased pulmonary capillary venous pressure has been referred to as the "syndrome pseudo-mitrale."[14] It is the purpose of this report to emphasize that this increase in the size of the left atrium may attain an unusual magnitude.

The radiologic cardiac silhouette is influenced not only by the anatomy of the heart but also by the physiology of the circulation. Thus, it is generally accepted that right atrial enlargement is a common concomitant of atrial septal defect,[3] although the mechanism underlying this increase in size is by no means clearly established. Studies of the relative elastic properties of the atria suggest that for equal volume increments the right atrial system is more distensible than the left.[15] Nevertheless, it is not surprising that the left atrium might respond with varying degrees of enlargement to the volume of blood delivered into it by the shunt of a patent ductus. In early observations on the effects of patent ductus arteriosus on the heart, Eppinger and Burwell[16] commented that "if a normal mitral valve is not wide enough to transmit this large amount of shunted blood without an elevated left atrial pressure, there may be visible dilatation of the left atrium. . . . One . . . patient before operation showed a mid-diastolic apical murmur characteristic of mitral stenosis. Since ligation of the ductus this murmur has never been heard." Left atrial enlargement of mild degree was described in 8 of their cases. In a study of the roentgenographic signs of 45 cases of patent ductus, left atrial enlargement was present in 32 cases.[17] Although the authors believed that enlargement of the left atrium was one of the most common signs of patent ductus, the degree of enlargement constituted, at most, a moderately prominent feature of the x-ray film. Two of Wood's cases of patent ductus had a P mitrale.[18] In another series of 73 cases,[19] 5 cases had bifid P waves, and 2 had fullness of the left atrium radiologically. Kjellberg and associates[3] diagnosed left atrial enlargement in 62 of 76 cases, and considered this a characteristic feature of patent ductus. Our case illustrates not only the unusual degree to which the left atrium can enlarge in patent ductus arteriosus (Fig. 2,*A*), but also the property of regression which follows surgical correction (Fig. 2,*B*). The apical diastolic murmur across a normal mitral valve[19] reflected an increase in mitral transvalvular flow associated with a pulmonary to systemic flow ratio of 5 to 1. The P wave of the electrocardiogram was typical of left atrial enlargement.

SUMMARY

A case is described of a 37-year-old woman with a large patent ductus arteriosus associated with unusual enlargement of the left atrium. Although significant left atrial enlargement is most commonly a reflection of organic mitral valve disease, the left atrium can nevertheless enlarge under the influence of a variety

of other stimuli, including left-to-right central shunts of the ductus type. The degree of enlargement in this case, however, clearly reached the proportion seen in mitral valve disease.

Dr. George Katter of Johnstown, Pa., kindly referred this patient for cardiac evaluation.

REFERENCES

1. Corvisart, J. N.: Essai sur les maladies et les lesions organiques du coeur et des gros vaisseaux, Paris, 1806, Migneret.
2. Rigler, L. G.: The Visualized Esophagus in the Diagnosis of Diseases of the Heart and Aorta, Am. J. Roentgenol. **21**:563, 1929.
3. Kjellberg, S. R., Mannheimer, E., Rudhe, V., and Jonsson, B.: Diagnosis of Congenital Heart Disease, Chicago, 1955, The Year Book Publishers, Inc.
4. Walther, R. J., Starkey, G. W., Zervopolus, E., and Gibbons, C. A.: Coronary Arteriovenous Fistula, Am. J. Med. **22**:213, 1957.
5. Brown, R. C., and Burnett, J. D.: Anomalous Channel Between Aorta and Right Ventricle, Pediatrics **3**:597, 1949.
6. Cobbs, B. W., Shillingford, J. P., and Steiner, R. E.: The Size of the Left Atrium in Conditions Other Than Mitral Valve Disease, Brit. Heart J. **19**:495, 1957.
7. Evans, W., and Jackson, F.: Constrictive Pericarditis, Brit. Heart J. **14**:53, 1952.
8. Baber, A.: Displacement of the Esophagus by Cardiac Lesions Other Than Mitral Stenosis, Am. Heart J. **13**:228, 1937.
9. Kroop, I. G., and Grishman, A.: Isolated Interventricular Septal Defect With Dilatation of the Pulmonary Artery, Am. Heart J. **40**:125, 1950.
10. Engle, M. A.: Ventricular Septal Defect in Infancy, Pediatrics **14**:16, 1954.
11. Parkinson, J.: Enlargement of the Heart, Lancet **1**:1392, 1936.
12. Parkinson, J.: The Radiology of Rheumatic Heart Disease, Lancet **1**:895, 1949.
13. Macruz, R., Perloff, J. K., and Case, R. B.: A Method for the Electrocardiographic Recognition of Atrial Enlargement, Circulation **17**:882, 1958.
14. Vernant, P., Norrarlle, J., Schweisguth, O., Labesse, J., Bouchard, F., Mathey, J., Binet, J., and Oustrieres, G.: Les canaux arteriels avec hypertension pulmonaire sans inversion du shunt, Arch. mal. coeur **48**:277, 1955.
15. Little, R. C.: Volume Elastic Properties of the Right and Left Atrium, Am. J. Physiol. **158**:237, 1949.
16. Eppinger, E. C., and Burwell, C. S.: The Mechanical Effects of Patent Ductus Arteriosus on the Heart, J.A.M.A. **115**:1262, 1940.
17. Donovan, M. S., Neuhauser, E. B. D., and Sosman, M.: Roentgen Signs of Patent Ductus Arteriosus, Am. J. Roentgenol. **50**:293, 1943.
18. Wood, P.: The Eisenmenger Syndrome, Brit. M. J. **2**:701 and 755, 1958.
19. Neill, C., and Mounsey, P.: Auscultation in Patent Ductus Arteriosus, Brit. Heart J. **20**:61, 1958.

Double Nodal Rhythm With A-V Dissociation

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Double nodal rhythm may be defined as the independent action of two pacemakers in the A-V junctional tissue: one pacemaker controls the atria and the other controls the ventricles. In reviewing the literature on double rhythms, we found only rare cases of possible double nodal rhythm.[1,1a-c]

The diagnosis is based upon the demonstration of A-V dissociation, inverted P waves in Leads II, III, and aV_F, and the supraventricular origin of the ventricular complex. A-V dissociation would exclude retrograde conduction from the ventricles, and thus, the A-V junctional area would be the origin of the atrial impulse formation (exceptions to be noted in the discussion). The A-V junction may be implicated as the pacemaker for the ventricle if one of two situations exists: (1) if the QRS pattern is narrow (less than 0.10 second) in all leads; or (2) if a bizarre QRS pattern (more than 0.10 second) is present which has been noted as an obviously conducted supraventricular impulse in another ECG.

The purpose of this paper is to present three examples of what appears to be double nodal rhythm with A-V dissociation. Each occurred in a different type of heart disease, and each manifested a different degree of A-V block. Case 2 is of particular interest because the two abnormal rhythms occurred in the course of digitalis intoxication.

CASE REPORTS

CASE 1.—A 4-year-old white girl has been followed up in the Maimonides Hospital Pediatric Cardiac Outpatient Department since the age of 6 months. The clinical and laboratory data suggest the presence of corrected transposition of the great vessels. Repeated electrocardiograms consistently revealed complete A-V dissociation, as depicted in Fig. 1. The P waves are inverted in Leads II, III, and aV_F, and are upright in Lead aV_R, suggesting a nodal pacemaker. The atrial cycle is regular and measures 0.45 second. There is independent ventricular activity; the ventricular cycle length is 0.72 second. The QRS is narrow in all leads (0.06 second), consistent with supraventricular origin of the ventricular action.

Comment.—We are dealing in this case with complete A-V dissociation in a child with congenital heart disease. The presence of an atrial rate distinctly faster than the ventricular rate, in the absence of ventricular captures, suggests ante-

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grade block. Because of the persistent presence of this arrhythmia since birth, one is inclined to consider complete A-V block rather than partial A-V block. The suspected cardiac lesion in this child (corrected transposition of the great vessels) has been reported in association with complete heart block.[2] The relatively rapid ventricular rate (85 per minute), on the other hand, does not speak against complete heart block, for the ventricular rate in congenital heart block is usually distinctly faster than that seen in arteriosclerotic heart disease.[3,4] For these reasons, then, it would seem that this case most likely represents double nodal rhythm with complete A-V block.

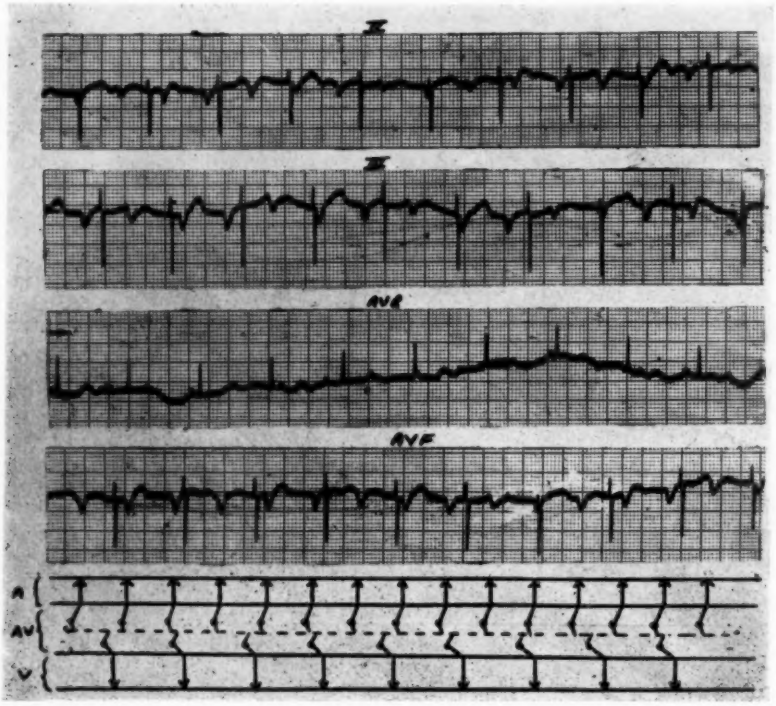

Fig. 1.—There is complete A-V dissociation. The P waves are inverted in Leads II, III, and aV_F and are upright in Lead aV_R. The atrial rhythm is regular. The atrial cycle length is 0.45 second. The ventricular rhythm is regular. The ventricular cycle length is 0.72 second. The tracing is believed to represent A-V dissociation in the presence of complete A-V block.

CASE 2.—A 43-year-old white woman with severe rheumatic heart disease was admitted to Maimonides Hospital in November, 1959, in acute respiratory distress despite strict adherence to a rigid medical regimen (digitalis, low-sodium diet, chlorothiazide, and occasional mercurial injection). Fig. 2 shows a continuous Lead II electrocardiogram. There is complete A-V dissociation. The atrial action is represented by inverted P waves, consistent with retrograde activation of the atria. The rate is regular at 96 per minute. The ventricular action is likewise regular, with a rate of 132 per minute. The QRS is somewhat bizarre, but similar in appearance to ventricular beats which were aberrantly conducted from the atria (Fig. 3,*B*).

Fig. 3,*A* was taken following the intravenous administration of potassium chloride. It reveals a regular ventricular rate of 125 per minute. Retrograde conduction to the atria is indicated by sharp indentations following the QRS complexes; this is not seen in a subsequent tracing of obviously conducted beats. Fig. 3,*B*, taken after further intravenous infusion of potassium chlo-

ride, reveals a regular sinus tachycardia of 150 per minute. In this tracing the P waves are upright and the QRS configuration is identical to that in Figs. 2 and 3,*A*, indicating that the QRS complex in Figs. 2 and 3,*A* is of supraventricular origin.

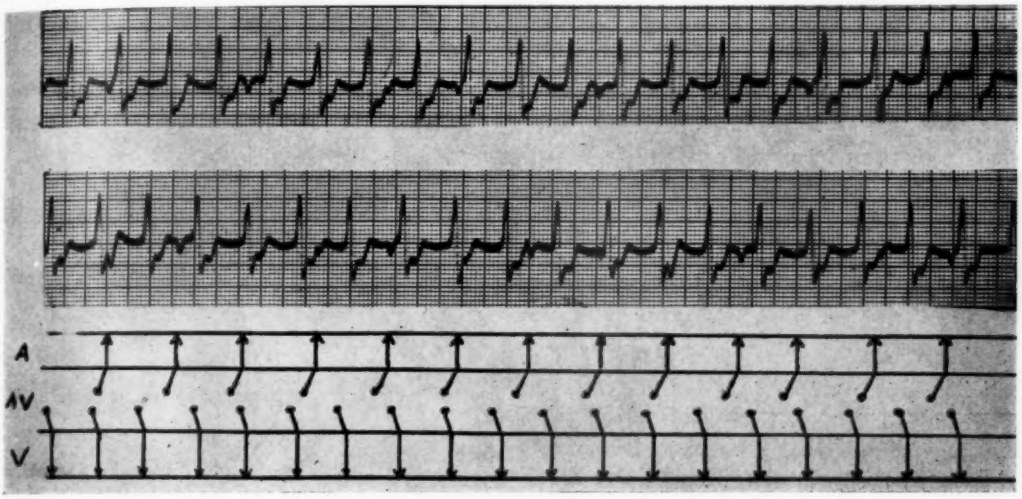

Fig. 2.—Continuous Lead II. There is complete A-V dissociation. The P waves are inverted, indicating retrograde activation of the atria. The atrial rhythm is regular. The atrial cycle length is 0.64 second. The ventricular rhythm is regular. The ventricular cycle length is 0.45 second. The QRS is bizarre in shape, representing aberration of intraventricular conduction. The tracing represents A-V dissociation secondary to interference of two nodal pacemakers within the A-V junction.

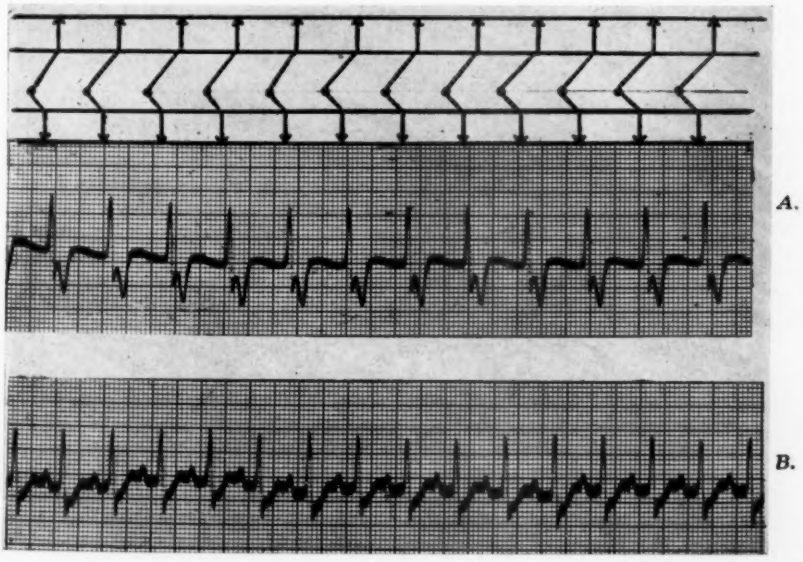

Fig. 3.—*A*, This demonstrates a regular ventricular rhythm (the ventricular cycle length is 0.48 second). The QRS is followed by an inverted P wave which represents retrograde activation of the atria. The QRS is of the same configuration as that seen in Fig. 2. The tracing represents a nodal tachycardia with bidirectional conduction to atria and ventricles as seen in the schematic diagram. *B*, The tracing shows a regular sinus tachycardia of 150 per minute. The QRS is of the same configuration as that seen in Figs. 2 and 3,*A*, verifying supraventricular origin of the QRS complex in those tracings.

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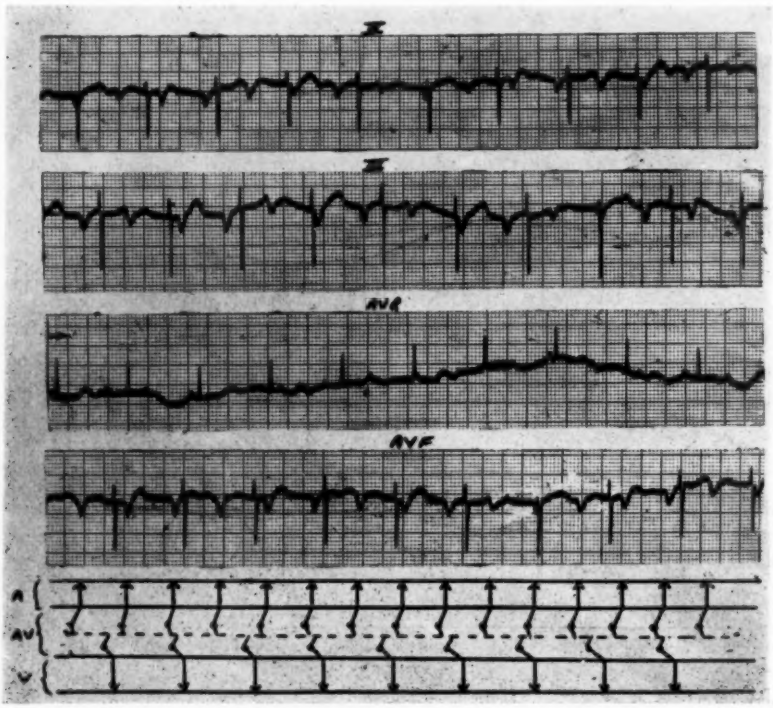

Fig. 1.—There is complete A-V dissociation. The P waves are inverted in Leads II, III, and aV$_F$ and are upright in Lead aV$_R$. The atrial rhythm is regular. The atrial cycle length is 0.45 second. The ventricular rhythm is regular. The ventricular cycle length is 0.72 second. The tracing is believed to represent A-V dissociation in the presence of complete A-V block.

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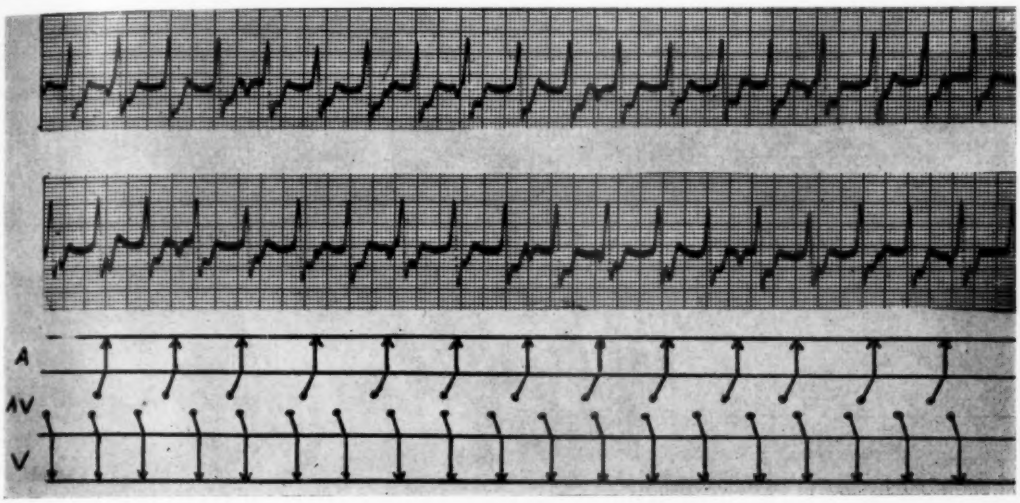

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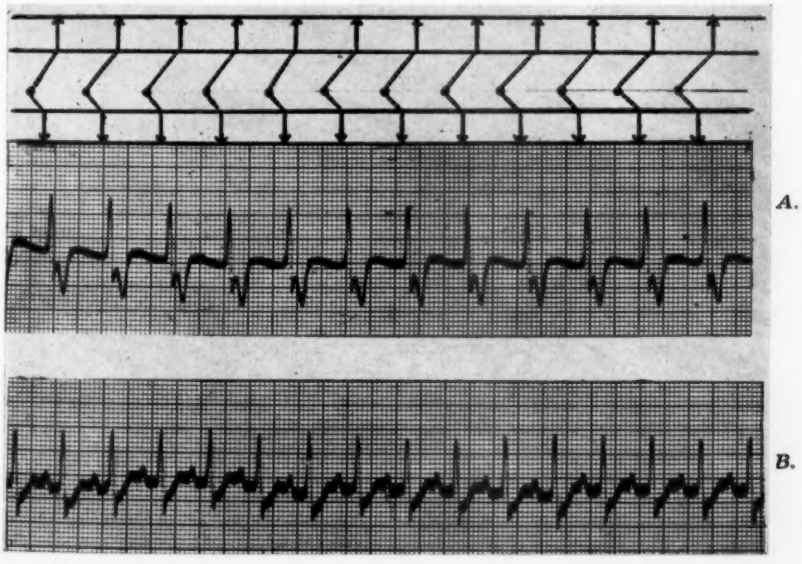

Fig. 3.—*A*, This demonstrates a regular ventricular rhythm (the ventricular cycle length is 0.48 second). The QRS is followed by an inverted P wave which represents retrograde activation of the atria. The QRS is of the same configuration as that seen in Fig. 2. The tracing represents a nodal tachycardia with bidirectional conduction to atria and ventricles as seen in the schematic diagram. *B*, The tracing shows a regular sinus tachycardia of 150 per minute. The QRS is of the same configuration as that seen in Figs. 2 and 3,*A*, verifying supraventricular origin of the QRS complex in those tracings.

Comment.—This patient with severe rheumatic heart disease and digitalis intoxication appears to have manifested a double nodal rhythm with A-V dissociation in the absence of significant A-V block. After the intravenous administration of potassium chloride, conduction developed bidirectionally (Fig. 3,*A*) and in an antegrade direction to the ventricles from a sinus pacemaker (Fig. 3,*B*). This is strong circumstantial evidence that a complete heart block did not exist. It would seem rather that the dissociation here is secondary to (1) interference in the A-V junction between the two (nodal) pacemakers, and (2) mild prolongation of the refractory period of the A-V junction secondary to digitalis effect.[5]

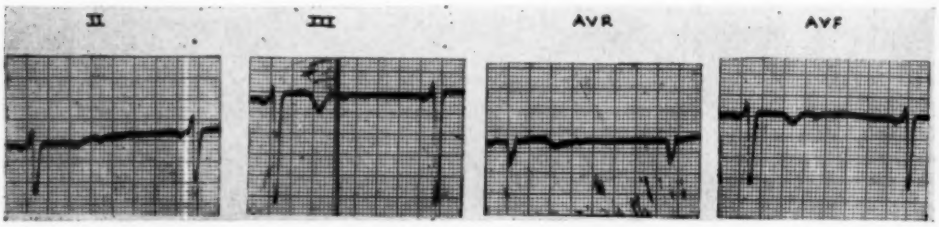

Fig. 4.—This tracing shows inverted P waves in Leads II, III, and aV_F, with a small upright P wave in Lead aV_R. The P-R interval is fixed at 0.10 second.

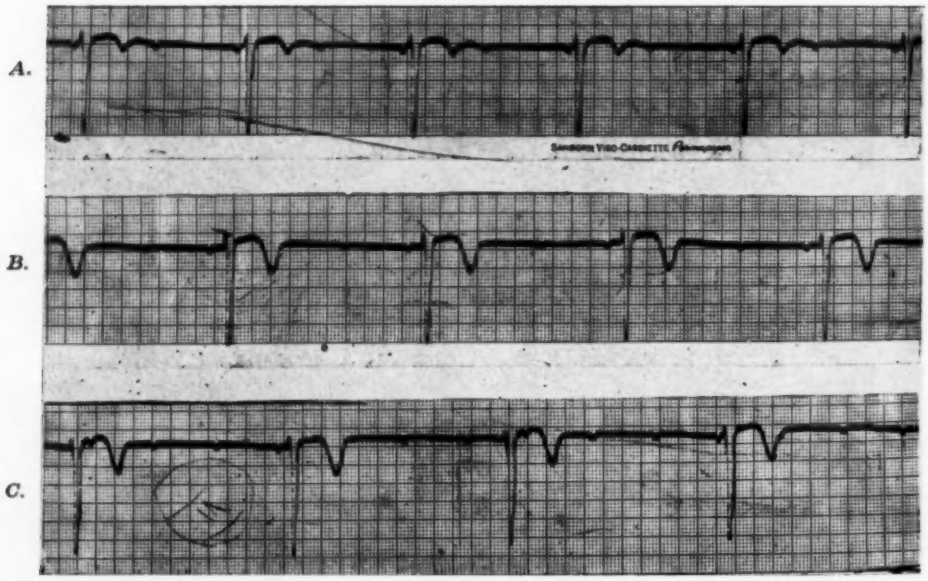

Fig. 5.—A series of three tracings (Lead III) taken over a period of 12 hours. *A*, The atrial (nodal) cycle length is 0.88 second. The ventricular cycle length is 1.76 seconds. The P-R interval is 0.10 second. This tracing represents regular nodal rhythm with full 1:1 retrograde conduction to the atria and 2:1 antegrade conduction to the ventricles. *B*, The atrial (nodal) cycle length has decreased to 0.70 second, with a resultant increase in the ventricular cycle length to 2.10 seconds. The P-R interval is 0.18 second, secondary to an increased delay in the antegrade conduction. This tracing represents regular nodal rhythm with full 1:1 retrograde conduction to the atria and 3:1 antegrade conduction to the ventricles. *C*, The atrial (nodal) rhythm is regular and the atrial cycle length is 0.65 second. The ventricular rhythm is regular with a ventricular cycle length of 2.32 seconds. There is complete A-V dissociation. This tracing represents double nodal rhythm with A-V dissociation in the presence of a high degree of A-V block.

The first effect of the potassium was the disappearance of the upper nodal rhythm. Note that the rate of the lower nodal rhythm remained essentially the same (125 per minute, as compared to 132 per minute). The disappearance of the upper nodal rhythm and the decrease in the refractory period of the A-V junction made it possible for the lower nodal rhythm to activate the atria in a retrograde direction. Final effect of the potassium was disappearance of the lower nodal rhythm, with resultant control of the ventricular activity by the sinus pacemaker.

CASE 3.—An 82-year-old white woman with known arteriosclerotic heart disease was admitted to Maimonides Hospital because of recurrent Adams-Stokes attacks. The limb lead electrocardiogram revealed inverted P waves in Leads II, III, and aV_F, with small upright P waves in Lead aV_R (Fig. 4). Fig. 5 shows a series of three tracings (Lead III) taken over a period of 12 hours. Fig. 5,*A* manifests regular atrial activity (the atrial cycle length is 0.88 second). There is a fixed P-R interval of 0.10 second and a regular ventricular rate (the ventricular cycle length is 1.76 seconds) which is one half that of the atrial rate. This apparently represents a regular nodal rhythm of 68 per minute with 2:1 antegrade block.

Fig. 5,*B* reveals a decrease in the atrial cycle length to 0.70 second, due to an increase in rate. The P-R interval has increased to 0.18 second, but remains fixed. The ventricular action is regular, with an increase in its cycle length to 2.10 seconds. This, therefore, represents a regular nodal rhythm of 86 per minute with full retrograde conduction to the atria and a 3:1 antegrade block.

Fig. 5,*C* demonstrates a further increase in the atrial rate (the atrial cycle length is 0.65 second); the P-R interval now varies. There is an independent ventricular rhythm (the ventricular cycle length is 2.32 seconds). The identical configuration of the QRS in both the conducted and the independent ventricular beats indicates its supraventricular origin. Fig. 5,*C*, therefore, represents A-V dissociation secondary to two nodal foci which control the atrial and ventricular activity independently.

Comment.—This patient manifested a decrease in antegrade conduction to the ventricles subsequent to an increase in the rate of the pacemaker. The somewhat prolonged P-R interval (0.18 second) in Fig. 5,*B* is consistent with nodal origin of the P waves, if there is a further delay in the antegrade conduction to the ventricles in excess of retrograde conduction to the atria.[6] In Fig. 5,*C*, a nodal focus developed as an escape mechanism to control the ventricular activity. This last tracing, then, represents double nodal rhythm with A-V dissociation, in the presence of a high degree of A-V block.

DISCUSSION

Double nodal rhythm with A-V dissociation (as the more usual forms of A-V dissociation) may be associated with (1) varying degrees of A-V block, (2) interference within the A-V junction, or (3) a combination of these mechanisms.[7] In addition, it may occur in forms of heart disease of various origin.

Inverted P waves have also been observed in experimentally induced low atrial extrasytoles,[8] low atrial tachycardias,[8] and in aberrant intra-atrial conduction.[10,11] Their electrocardiographic differentiation, however, from A-V nodal rhythm with retrograde conduction is frequently difficult, and is based primarily upon the length of the P-R interval. In the presence of A-V dissociation, this point of differentiation is obviously not applicable.

Main stem extrasystoles[12] and pacemaker activity occurring in the ventricles above the bifurcation of the bundle have also been described.[13] In the presence of A-V dissociation, with loss of fixed temporal relationships between P and R, the differential diagnosis on an electrocardiographic basis is impossible.

SUMMARY

1. Three cases of what appear to be double nodal rhythm are presented The diagnosis is based upon A-V dissociation, inverted P waves in Leads II, III, and aV_F, and the demonstration of a supraventricular pacemaker for the ventricles. The exact differentiation between the inverted P waves of a nodal pacemaker and those of a low atrial pacemaker or sinus pacemaker with aberrant intra-atrial conduction cannot be made in the presence of A-V dissociation.

2. One case is of particular interest because the two abnormal rhythms appeared in the course of digitalis intoxication.

We are indebted to Dr. William Dressler for his guidance in the preparation of this paper.

REFERENCES

1. Bix, H. H.: A-V Nodal Rhythm With Various Types of A-V Block, J. Mt. Sinai Hosp. **2**:42, 1953.
1a. Castellanos, A., Jr., and Calviño, J. M.: Dissociation With Interference Between Pacemakers Located Within the A-V Conducting System, AM. HEART J. **56**:562, 1958.
1b. Schott, A.: Atrioventricular Rhythm With and Without Retrograde Block, AM. HEART J. **13**:61, 1937.
1c. Luten, D., and Jensen, J.: Ventricular Bigeminy (Parasystole or Reciprocal Rhythm) in Atrioventricular Rhythm, AM. HEART J. **7**:593, 1932.
2. Wacken, W., Cooley, D. A., McNamara, D., and Moser, R. H.: Corrected Transposition of the Great Vessels, Atrioventricular Heart Block, and Ventricular Septal Defect, Circulation **17**:249, 1958.
3. Katz, L. N., and Pick, A.: Clinical Electrocardiography. The Arrhythmias, Philadelphia, 1956, Lea & Febiger.
4. Paul, M. H., Rudolph, A. M., and Nadas, A. S.: Congenital Complete Atrioventricular Block: Problems of Clinical Assessment, Circulation **18**:183, 1958.
5. Lown, B., and Levine, H. D.: Atrial Arrhythmia, Digitalis and Potassium, New York, 1958, Landsberger Medical Books, Inc.
6. Langendorf, R., Simons, A., and Katz, L. N.: A-V Block in A-V Nodal Rhythm, AM. HEART J. **27**:209, 1944.
7. Dressler, W., Roesler, H., and Specter, L. S.: Dissociation With Interference in the Presence of 2:1 Atrioventricular Block, AM. HEART J. **44**:238, 1952.
8. Prinzmetal, M., Corday, E., Brill, I. C., Oblath, R. W., and Kruger, H. E.: The Auricular Arrhythmias, Springfield, Ill., 1952, Charles C Thomas, Publisher.
9. Scherf, D., and Gurbuzer, B.: Further Studies on Coronary Sinus Rhythm, Am. J. Cardiol. **2**:579, 1958.
10. Scherf, D., and Schott, A.: Extrasystoles and Allied Arrhythmias, London 1953, William Heinemann Medical Books, Ltd.
11. Lown, B., Wyatt, N. F., and Levine, H. D.: Paroxysmal Atrial Tachycardia With Block, Circulation **21**:129, 1960.
12. Marriott, H. J. L., and Bradley, S. M.: Main Stem Extrasystoles, Circulation **16**:544, 1957.
13. Langendorf, R., and Katz, L. N.: Unusual Arrhythmias due to Multiple Sites of Conduction Delay in the A-V Junction in Cases With a Subsidiary Ventricular Pacemaker Located Above the Bifurcation of the Common Bundle, AM. HEART J. **24**:31, 1942.

Periarteritis in a 4-Month-Old Infant Unresponsive to Penicillinase

M. J. Henry, M.D., H. G. E. Stoeckle, M.D.,* and H. C. Hopps, M.D.***
Galveston, Tex.

Until recently, periarteritis nodosa was considered to be rare in infants under 1 year of age. However, Munro-Faure[1] reviewed 19 cases which occurred in this age period, and in 12 of these cases, involvement of the coronary arteries and thrombosis were dramatic aspects. In addition to similar involvement of the coronary arteries the case presented here shows some unique features.

CASE REPORT

History.—J. D., a white male, was hospitalized on the pediatric service of the University of Texas Medical Branch Hospitals when he was 4 months old, with an illness which had lasted 15 days. Gestation, labor and delivery, and neonatal history were normal. When he was 2 months old, the infant had a transient skin eruption, possibly related to ingestion of peaches. At about this same time he received oral iron therapy for anemia. When he was 3½ months old, he developed an acute episode of fever, nasal congestion, irritability, and, after antibiotic therapy, a fine papular eruption on the trunk. He developed cough, loose stools, and a bright redness of the palms after oral penicillin. Fever persisted and the infant was hospitalized by the family physician at another institution on the fourth day of illness. Hemoglobin at that time was 8.5 Gm. per cent, and the white blood cell count was 15,750/mm.^{3}, with a slight left shift in differential count. Blood culture, urinalysis, chest roentgenograms, and intravenous urogram showed no abnormality. Treatment included penicillin, streptomycin, sulfisoxazole, kanamycin, chloramphenicol, and blood transfusion. Response was satisfactory, but on the fifteenth day of illness the infant developed a rise in temperature to 104°F., a fine, maculopapular eruption over the entire body, and a moderate pitting edema below the knees. He was then transferred to the University of Texas Medical Branch Hospitals.

Physical Findings.—The patient weighed 5.7 kilograms, and was 77 cm. in length. Blood pressure was 130-180/100-110 mm. Hg, temperature was 101°F. rectally, respiratory rate was 60 per minute, and pulse was 140 per minute. The infant was at times very irritable and at times lethargic. The skin was involved with a blotchy, erythematous, macular eruption, evanescent in character, sometimes appearing and disappearing with 30 minutes. The eruption did not involve the diaper area or areas of skin in contact with bed linen, but this distribution was apparently not a manifestation of light sensitivity. The hands and feet were erythematous, with patchy areas of cyanosis. At times, one or more fingers would appear cyanotic at the same time that other digits of the same hand appeared flushed. There was a moderate pitting edema of the lower ex-

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tremities. The margin of the liver was palpated 4 cm. below the costal margin. Except for a mucopurulent nasal discharge and moderate conjunctival injection there were no other abnormalities.

Laboratory Investigations.—Peripheral blood counts showed the hemoglobin to be 11.5 to 14.3 Gm. per cent; the white blood cell count was 25,000 to 73,000/mm.^{3}, with differential white cell counts of 60 to 70 per cent polymorphs, 10 to 20 per cent lymphocytes, 3 to 5 per cent stab forms, and 1 to 2 per cent eosinophils. Platelet count was 530,000/mm.^{3}. Urinalyses were normal except for 2 or 3 red blood cells and 3 or 4 white blood cells per high-power field in each specimen, and 1+ protein in one specimen. Culture of urine yielded coliform organisms. Blood culture and serologic test for syphilis were negative. Blood urea nitrogen and serum sodium, potassium, chloride, and carbon-dioxide combining power were normal. Roentgenograms of the chest showed no abnormality. Electrocardiogram showed a 3 to 4 mm. Q wave in Leads II and III. A small R wave in Lead V_1 and a tall R wave in Lead V_6 were interpreted as indicating left ventricular preponderance.

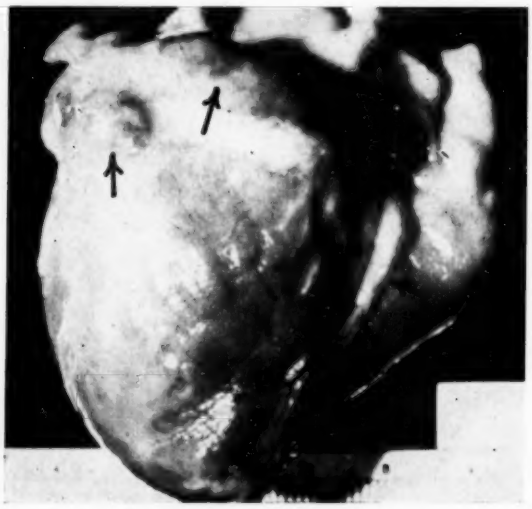

Fig. 1.—Heart, showing tremendous dilatation of coronary arteries.

Hospital Course and Treatment.—The infant's hospital course was marked by persistence of the findings enumerated above, with elevations of temperature to 103°F. No drug therapy was given, except for 800,000 units of penicillinase on two occasions. This therapy was given on the basis of the clinical impression of suspected hypersensitivity angiitis, with the knowledge that penicillinase may, itself, produce hypersensitivity reactions.[10,11] This therapy resulted in no apparent change in the infant's condition. Two days before death the infant's femoral pulses were observed to be weak. On the fifth hospital day the infant developed a shock-like state and died in spite of emergency supportive measures.

Autopsy Findings.—

Gross findings: The appearance of the infant was not remarkable except for moderate edema of the lower extremities and cyanosis of the nail beds. The lungs exhibited moderate congestion, slight edema, and occasional small foci of atelectasis. The pericardial cavity contained approximately 60 ml. of xanthrochromic fluid, and there were fibrous adhesions over most of the left ventricle and the left atrium, especially along the course of the left coronary artery. The heart weighed 40 grams (normal average, 27 grams, at this age[2]). The most striking change was marked dilatation and tortuosity of both the right and left coronary arteries (Fig. 1). In addition to the diffuse dilatation there were nodular foci of more marked aneurysmal dilatation. The right coronary artery had an average diameter of 0.6 cm., and was occluded by recently formed thrombus (Fig. 2). The anterior descending branch of the left coronary artery had an average diameter of 0.4 cm. in its proximal two thirds, and there was a recently formed occlusive thrombus involving the

proximal 0.8 cm. segment. Circumflex arteries presented several nodular aneurysmal dilatations with diameters as large as 0.6 cm. One of these was filled with recently formed thrombus. Except for the terminal 1 cm. of the abdominal aorta and the proximal 3 cm. of the right iliac artery, which were completely filled with recently formed thrombus (Fig. 3), other major blood vessels appeared grossly to be normal.

The kidneys were paler than usual. There were two infarcts in the left kidney and one in the right, averaging 0.5 cm. in diameter.

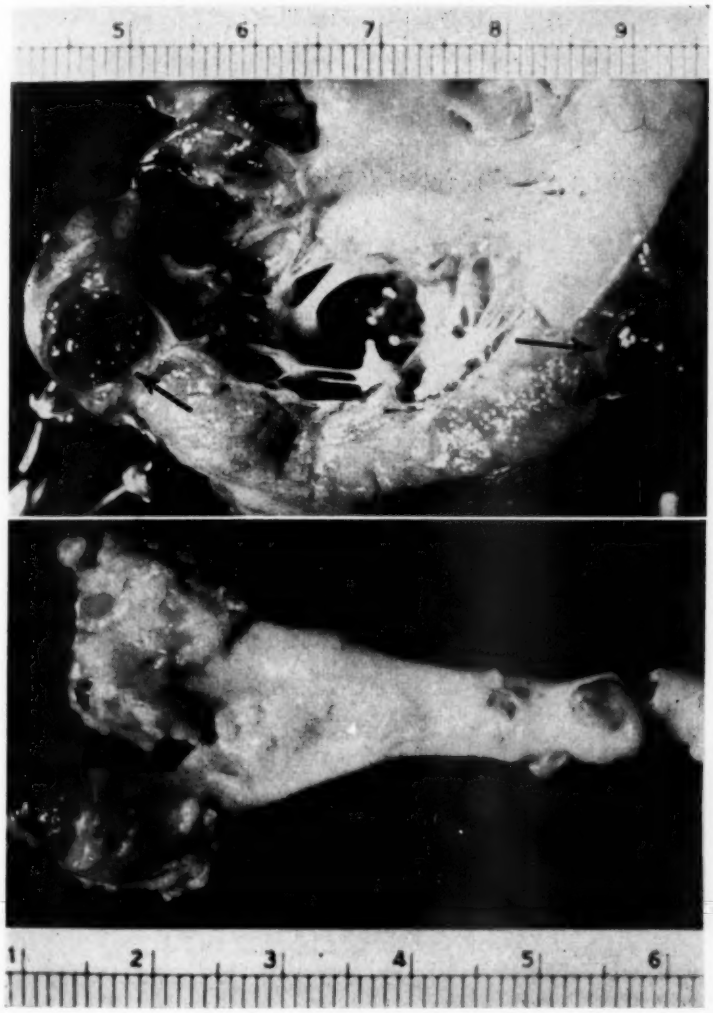

Fig. 2.

Fig. 3.

Fig. 2.—Cross section of a dilated coronary artery, showing occlusion of lumen by thrombus.
Fig. 3.—Thrombosed iliac artery and terminal aorta.

Histopathology: Microscopic study of the lungs revealed slight bronchopneumonia in addition to edema and congestion. There were large foci of slight interstitial myocarditis associated with moderate interstitial edema. Some of these foci were adjacent to large, inflammed arteries, but foci were also present elsewhere. There were no granulomatous foci within the myocardium, nor other changes suggesting rheumatic myocarditis. Major coronary arteries exhibited marked, diffuse inflammation which involved all layers and extended for a considerable distance into the subepicardium and epicardium (Fig. 4). It appeared that the fibrinous epicarditis had its origin

in this manner. The occlusive thrombi which were contained within inflammed vessels were very rich in erythrocytes and did not appear to be septic. At several sites there were foci of beginning organization. Elastic tissue stains demonstrated disruption of the elastica, with large segments of arterial wall devoid of recognizable elastic tissue, particularly in the most dilated portions of the inflammed coronary arteries.

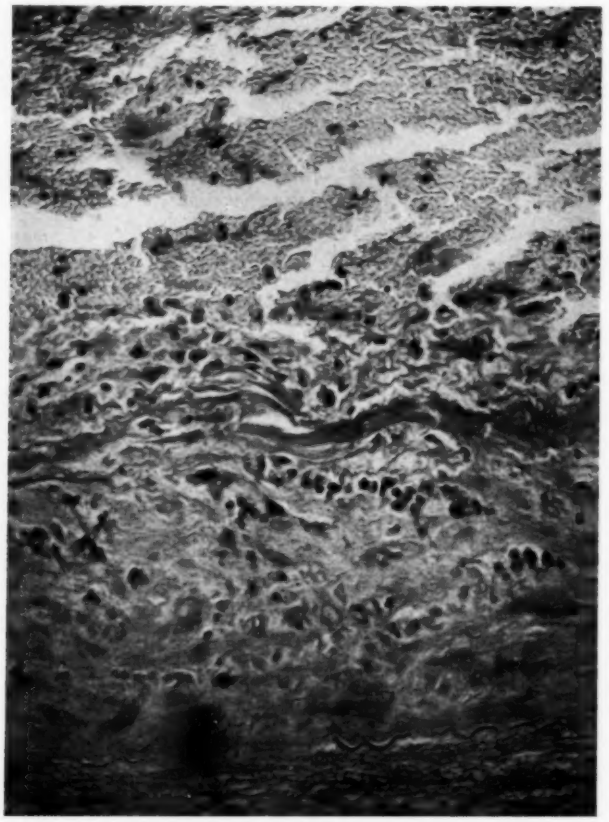

Fig. 4.—Section of coronary artery, showing cellular infiltrates, fragmented elastic laminae, and disarrangement of normal architecture (hematoxylin and eosin ×230).

Within coronary arteries an intense inflammatory reaction dominated the picture, in contrast to the reaction in several small arteries of the adrenal and of the kidney, in which inflammatory cellular reaction was less marked but fibrinoid necrosis was striking (Fig. 5), suggesting an earlier state in the pathogenesis of the process. Here, too, elastic tissue stains demonstrated fraying and splitting of fibers, with small, patchy foci from which elastica had completely disappeared. The infarcts in the kidneys were recent and bland and bore a direct relationship to the several arteries there which exhibited acute periarteritis. An analysis of liver and muscle for mercury was negative.

DISCUSSION

The cause of periarteritis nodosa has been the subject of much conjecture. Rich[3] was able to induce serum sickness in rabbits and demonstrate arterial involvement consistent with periarteritis nodosa. Heptinstall and Germuth[4] found that in short periods of sensitization in experimental animals the arteries

of the heart and mesentery are more frequently involved than in chronic sensitivity states. Others[5-7] have implicated hypertension as a precipitating cause of the arterial changes. Goldberger[5] proposed an interrelationship between hypertension and renal and endocrine factors as the underlying mechanism. Rose[8] has implicated the hypersensitivity which results from beta-hemolytic streptococcus infections as a precipitating or contributing factor.

Hypertension was not mentioned in Munro-Faure's review[1] of periarteritis nodosa in infants. A resurvey of 17 of these 19 cases revealed no mention of hypertension. The original reports of the other 2 cases were unavailable for review. Renal arterial lesions were found at autopsy in all 7 cases with the generalized form of the disease, but were mentioned in only 2 of the 12 cases with predominant involvement of the coronary arteries. Rose[8,9] believes that hypertension is present only in the healing or healed stages of lesions of the renal vessels.

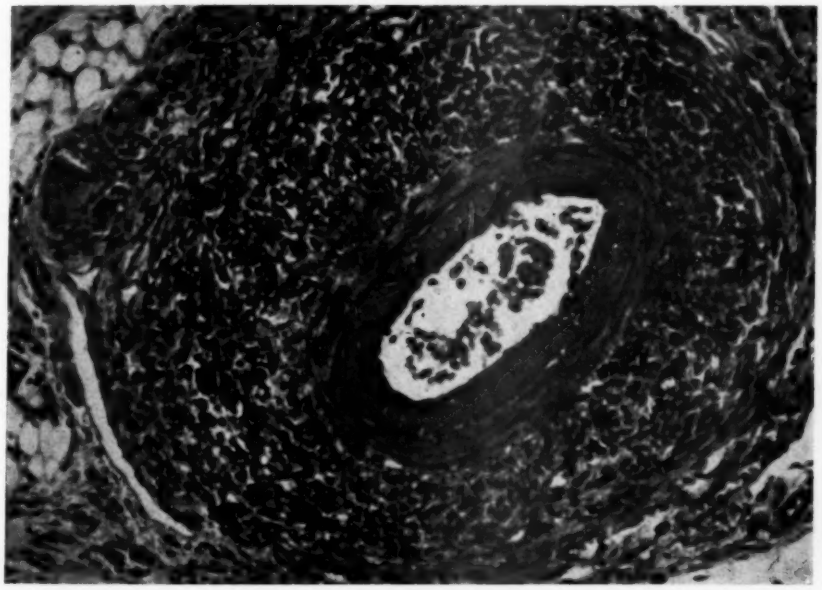

Fig. 5.—Coronary artery, showing marked inflammatory changes through entire vessel wall (hematoxylin and eosin ×200).

This infant exhibited most of the findings which are considered to be characteristic of periarteritis nodosa. The initial episode suggested an infection of the upper respiratory tract. There was an episode of suspected sensitivity to food. A skin eruption followed the administration of antibiotics, and suggested a drug sensitivity. There was a progressive anemia and marked leukocytosis. Striking hypertension was present without appreciable hematuria, an unusual feature. After a short period of improvement there was a rapidly fatal deterioration. Involvement of coronary arteries and other large arteries was marked, a common finding in periarteritis nodosa in infants.

SUMMARY

A case of periarteritis nodosa in a 4-month-old infant with marked involvement of cornary and other arteries is presented. Hypertension, fever, leukocytosis, and a recurring, evanescent skin eruption were the outstanding clinical features. Penicillinase did not alter the clinical course.

REFERENCES

1. Munro-Faure, H.: Necrotizing Arteries of the Coronary Vessels in Infancy, Pediatrics **23**:914, 1959.
2. Copoletta, J. M., and Wolbach, S. B.: Body Length and Organ Weights of Infants and Children. A Study of the Body Length and Normal Weights of the More Important Vital Organs of the Body Between Birth and 12 Years of Age, Am. J. Path. **9**:55, 1933.
3. Rich, A. R., and Gregory, L. E.: The Experimental Demonstration That Periarteritis Nodosa Is a Manifestation of Hypersensitivity, Bull. Johns Hopkins Hosp. **72**:65, 1942.
4. Heptinstall, R. H., and Germuth, F. G., Jr.: Experimental Studies on the Immunological and Histological Effects of Prolonged Exposure to Antigen. I. Distribution of Allergic Lesions Following Multiple Injections of Bovine Albumin, Bovine Gamma Globulin and Albumin and Globulin Together, With Special Reference to Granulomatous Arteritis, Bull. Johns Hopkins Hosp. **100**:71, 1957.
5. Goldberger, E.: Etiology and Pathogenesis of Syndromes Associated With Periarteritis Nodosa Lesions, Am. J. Cardiol. **3**:656, 1959.
6. Zeek, P. M.: Periarteritis Nodosa and Other Forms of Necrotizing Angiitis, New England J. Med. **248**:764, 1953.
7. Zeek, P. M.: Periarteritis Nodosa, Am. J. Clin. Path. **22**:777, 1952.
8. Rose, G. A., and Spencer, A.: Polyarteritis Nodosa, Quart. J. Med., new series **26**:43, 1957.
9. Bywaters, E. G. L., Rose, G. A., Wright, G. P., and Long, D. A.: Section of Experimental Medicine and Therapeutics, Proc. Roy. Soc. Med. **49**:287, 1956.
10. Weiss, R. C., and Crepea, S. B.: Sensitivity to Penicillinase, J. Allergy **30**:337, 1959.
11. Hyman, A. L.: Anaphylactic Shock After Therapy With Penicillinase, J.A.M.A. **169**:593, 1959.

Clinical-Pathologic Conference*

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CLINICAL ABSTRACT

History.—The patient was a 20-year-old Southern-born Negro girl who was admitted to the University of Illinois Research and Educational Hospitals for the second time 2 weeks before her death, with complaints of progressive weakness and shortness of breath. She was well until 16 months before her death, when she noted gradual onset of anorexia, loss of weight, dyspnea on exertion, and low-grade fever. She was hospitalized at Cook County Hospital, where work-up revealed the following: fever, cervical adenopathy, hemoglobin of 50 per cent, with normal urine, normal liver functions but slight hepatomegaly (2 FB), positive tuberculin test 1:1000, positive histoplasmin skin test, negative sickle cell and lupus erythematosus preparation, negative agglutinins for Brucella, typhoid and paratyphoid, IVP exhibited clubbing and widening of the infundibulum and calyces on the right, normal chest x-ray film, and node biopsy revealing "chronic lymphadenitis." Blood cultures and cultures of sputum, urine, and node for tuberculosis showed no growth. She received antituberculous drugs for 34 days, without remission, and signed out of the hospital. After leaving Cook County Hospital, all symptoms gradually worsened, and she became aware of a feeling of intense pressure in the epigastrium and substernal area which regularly occurred with exertion, forced her to sit down, and went away in a few minutes with rest. Physical examination on her first admission to the University of Illinois Research and Educational Hospitals was essentially unchanged from that at Cook County Hospital, except that she now exhibited a Grade 1 to 2 aortic blowing systolic murmur, with radiation to the neck. Laboratory findings were essentially unchanged except that the albumin-globulin ratio was 5/4.1 Gm. per cent, antistreptolysin-O titer was 125 units, thymol turbidity was 6.2 units, and a chest x-ray film now revealed moderate cardiac enlargement with suggestive evidence of right ventricular hypertrophy or mediastinal mass. Upper gastrointestinal series, and small bowel and barium enema series were within normal limits. The patient was uncooperative, refused other procedures, and, in the absence of a definitive diagnosis, was discharged, to be followed up in the Medical Residents Clinic. She was followed up as an outpatient without specific therapy for 6 months. Some arthralgia was noted during this time, venous pressure and circulation time were normal, and fluoroscopy suggested left ventricular hypertrophy. She was readmitted because of severe dyspnea which had lasted for 4 days.

Physical Examination.—Respirations were 30, temperature was 101.2° F., pulse was 130, and blood pressure was 110/60 mm. Hg. She was dyspneic and orthopneic. There was no cyanosis, and questionable slight distention of the neck veins. The lungs were clear to percussion and auscultation. The heart was enlarged to the mid-axillary line in the fifth intercostal space on the left, and a systolic thrill was felt at the apex. There was a Grade 3 harsh systolic murmur at the apex,

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with a presystolic gallop. A questionable short, high-pitched, mid-disatolic murmur was heard at the apex. There was a Grade 3 systolic harsh murmur over the aortic area and a short, high-pitched murmur, Grade 1 to 2 in early diastole over the aortic area. The liver was felt 3 finger-breadths below the costal margin, The remainder of the examination was not remarkable.

Laboratory Data.—Hemoglobin was 6.5 Gm. per cent; hematocrit, 37 per cent; white blood cell count, 7,600 with normal differential. Urinalysis, done only once, was within normal limits. A serologic test for syphilis which was made in the Outpatient Department was negative. Serologic tests for warm and cold agglutinins were negative; electrolytes were within normal limits; Ca, 4.3 mEq./L., alkaline phosphatase, 5.8 units; albumin-globulin ratio, 3.3/4.8 Gm. per cent; antistreptolysin-O titer, 833 units; bone marrow showed a normoblastic hypercellular marrow, and several blood and sputum cultures revealed no growth. Complement fixation tests for blastomycosis, coccidioidomycosis, and histoplasmosis were negative. Chest x-ray films indicated a bilateral, diffuse, infiltrative process, slight cardiomegaly, and a slight prominence of the aortic arch.

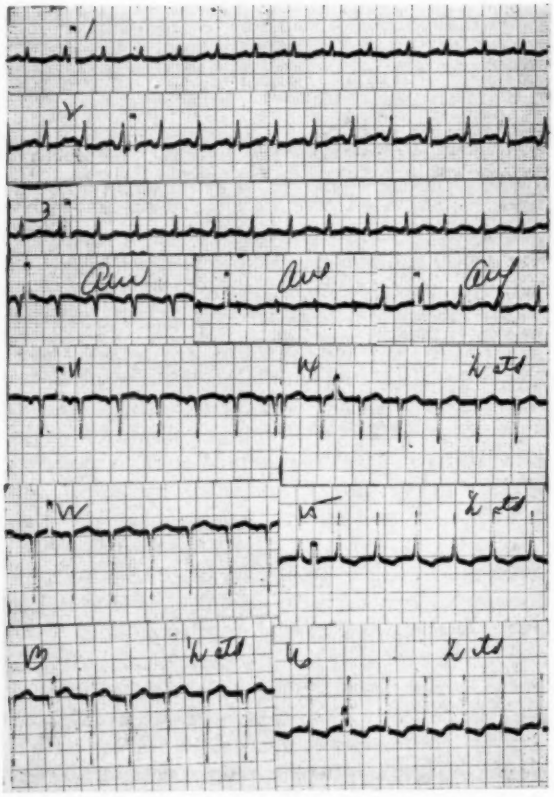

Fig. 1.—ECG showing left ventricular hypertrophy and possible septal infarction. (Leads I, II, III, aV_R, aV_L, aV_F, V_1, V_2 are slightly understandardized; V_3 through V_6 are approximately one half standardized.)

Hospital Course.—On the second hospital day, water-hammer pulses in the lower extremities were noted. She was digitalized and given nasal oxygen, with no improvement. Blood transfusions likewise did not improve her state. On the twelfth hospital day, she complained of right upper abdominal and flank pain. There was local tenderness but the abdomen was soft. The following day, moist cracking râles were heard at both lung bases, and venous distention in the neck increased. The aortic murmur became louder. The ECG was compatible with left ventricular hypertrophy and possible septal infarction (Fig. 1). The right-sided pain and dyspnea worsened, and she was found dead on the fourteenth hospital day.

DISCUSSION

DR. HARVEY: Our x-ray studies are related to the two separate hospital admissions of this patient; the interval between hospitalizations was 8 months. On both admissions the chief interest was in the chest, although the gastrointestinal, urinary, and skeletal systems were surveyed during the first hospital stay.

The first posteroanterior and left lateral chest films showed a moderate cardiomegaly which seemed to be generalized but was possibly a little more prominent in the right ventricular area on the lateral view. The ascending aorta was moderately dilated and the aortic knob slightly straightened. Both of these aortic changes must be highly significant in view of the fact that the patient was only 20 years of age. I see nothing further about the aorta or rib cage to suggest a coarctation of the aorta, and the cardiac contour was not typical. The lungs, diaphragms, pleural areas, and bones appeared to be normal. The soft tissues were extremely thin.

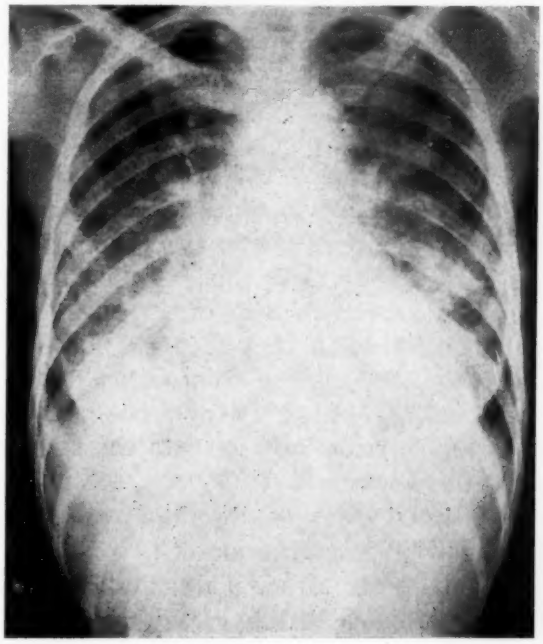

Fig. 2.—Chest film which shows diffuse mottling of the lungs due to suspected patches of consolidation, and evidence of cardiomegaly with aortic prominence.

Eight months later the chest showed striking changes in the lung fields (Fig. 2). There was a diffuse mottling due to what appeared to be patchy areas of consolidation. The changes were heavier in the central zones and faded out in the periphery. There was no apparent lymphadenopathy. The pleural zone in the right lateral base showed just a tiny amount of thickening, probably due to a very small amount of fluid. The heart and aorta were slightly more prominent than at the earlier examination. Our impression was that, aside from the cardiovascular changes, we were dealing with some type of infiltrative process, granulomatous change, or unusual congestive process related to the cardiovascular changes.

One week later, a terminal chest film was taken and showed quite a marked increase in central pulmonary density and the density in the medial base, but in a more conglomerate pattern, suggesting a superimposed pulmonary edema.

DR. ROBERG: When this young woman entered Cook County Hospital 16 months before her death, neither her symptoms nor the physical examination suggested localized disease. The shortness of breath on exertion was consistent with fever, anemia, and malaise. Upon physical examination, there was only mild enlargement of the liver and of the cervical lymph nodes. The red blood cells did not show sickling. If the fever, loss of weight, and anemia were caused by systemic lupus erythematosus, one could expect the demonstration of the lupus erythematosus phenomenon. The normal roentgenogram of the chest rendered tuberculosis, histoplasmosis, and sarcoidosis improbable. The decision to treat the patient as if she had hematogenous tuberculosis was reasonable: (1) the collecting system of the right kidney was abnormal; (2) cultures of the blood, sputum, urine, and lymph node yielded no growth; (3) dyspnea, fever, anemia, lymphadenopathy, and hepatomegaly were consistent with disseminated tuberculosis. The failure of 34 days of antituberculous therapy to bring improvement, however, made the tentative diagnosis of disseminated tuberculosis highly improbable.

We are confronted with the problem of fever of unknown cause in a young woman. It is probable that she refused to allow a biopsy of the liver, which would have been helpful with respect to infectious and neoplastic granulomatous disease. There was no clear evidence of bacterial, tuberculous, or fungal infection. Among the "collagen" diseases, systemic lupus erythematosus is unlikely. Hodgkin's disease, despite the nonspecific nature of the removed lymph node and the normal chest x-ray film, could explain only the early phase of her illness.

After leaving the hospital against advice, she continued to suffer from dyspnea, weakness, and fever. During the coming months, she developed intense, pressing distress in the epigastrium and deep to the sterum. This distress was precipitated by exertion and was relieved by rest. Despite her age and her sex, such distress must be accepted as representing the pain of either coronary artery insufficiency or of pulmonary hypertension.

Nine months after the onset of her illness and 7 months before death, she entered the University of Illinois Research and Educational Hospitals for the first time. Now, for the first time, there was evidence of localized disease: there was a systolic murmur in the aortic area which radiated into the neck, and the heart was moderately enlarged. The basal systolic murmur and the pain, which is consistent with angina pectoris, suggest disease of the aorta which is narrowing the coronary ostia. The serum globulin of 4.1 Gm./100 c.c. tells no more than does the fever: that she was suffering from some chronic inflammatory disease. The patient again left the hospital against advice. As an outpatient, her course was essentially unchanged. Four days before readmission, and 16 days before death, she became severely dyspneic.

Upon admission she was dyspneic, orthopneic, and febrile, with a pulse of 130 per minute. The blood pressure was 110/60 mm. Hg. The lungs were clear upon physical examination, but x-ray examination showed diffuse bilateral in-

filtration. This discrepancy suggests that there was interstitial infiltration of the lungs without the congestion of myocardial insufficiency. There was another discrepancy: the examiner considered the heart to be greatly enlarged, but the radiologist stated that there was only "slight cardiomegaly and slight prominence of the aortic arch." This suggests that the heart was beating violently, and that the examiner was misled by the diffuse shock transmitted to the wall of the chest. If he had sought carefully for the point of maximal impulse, he might not have been misled into believing that the cardiac apex was in the mid-axillary line. The harsh systolic murmur and the short, high-pitched diastolic murmur probably originated from the aortic valve and were heard also at the apex. The ECG, which showed left ventricular hypertrophy, was consistent with either aortic or mitral valvular disease. The laboratory studies were again normal except for the anemia. The normal white blood cell count and a second series of negative blood cultures removed bacterial endocarditis from serious consideration.

The patient failed rapidly. The water-hammer pulse, noted on the second day, indicates free aortic regurgitation. The failure to benefit from blood transfusion, digitalis, and oxygen is consistent with an inexorably progressive burden upon a failing heart. On the twelfth day, there was severe right upper abdominal and flank pain, which may represent renal infarction, rupture of a renal artery, or dissection of the abdominal aorta. On the thirteenth day, the aortic murmur was still louder, congestive failure developed, and the ECG was considered to indicate left ventricular hypertrophy and possible septal infarction. The combination of progressive aortic insufficiency and myocardial infarction would well explain the intractable myocardial failure. Death occurred on the fourteenth day, after increasing flank pain and dyspnea.

This young woman's illness of 16 months was characterized throughout by fever, anemia, and dyspnea on exertion. Toward the middle of the course of illness, angina pectoris developed. By the ninth month there was an aortic systolic murmur, and during the last month, rapidly progressive aortic insufficiency and congestive heart failure developed. Only four features are definite: fever, anemia, angina pectoris, and aortic regurgitation. The angina pectoris preceded the development of aortic insufficiency, which leads me to believe that the disease affected primarily the aorta, and only secondarily the aortic valves. The prolonged fever and anemia suggest that the primary disease is either sufficiently severe or diffuse enough to cause a systemic response.

The differential diagnosis is, then, that of diseases of the aorta and coronary arteries occurring in young persons. Furthermore, of those diseases which can lead to aortic valvular insufficiency, Marfan's syndrome or an isolated medial cystic necrosis can distort the coronary artery orifices and can lead to prolapse of the aortic valves. Aneurysms of the sinuses of Valsalva may cause aortic insufficiency, and one must consider the possibility that the final "aortic insufficiency" represented a fistulous connection between a sinus of Valsalva and the right side of the heart. This, however, is improbable. Clear evidence of congestive failure should have been evident at the time of her final hospital admission. Neither congenital nor acquired syphilis should have so rapid a course. And, moreover, none of these conditions are associated with fever and anemia.

Bacterial endocarditis cannot be considered seriously. Two series of blood cultures, one early and one late in her disease, were negative. No murmur was heard until she had been seriously ill for at least 6 months. No embolic phenomena were noted, and the urinalyses were normal.

Should we consider some disease which affected primarily the myocardium, leading to dilatation of the aortic ring and thus to aortic valvular incompetence? The only common form of myocarditis would be that of rheumatic fever. If our patient had had severe rheumatic myocarditis, there should have been cardiomegaly and murmurs at the time of her first hospitalization. Rheumatic myocarditis and arteritis, accompanying disease so intense as to cause fever and anemia for 16 months, should have led to earlier evidence of severe heart disease, if not to earlier death. Myocardial infiltration by either sarcoid or by amyloid is improbable in the absence of other evidence of either disease. Neither of them, without widespread distribution or complicating disease, is a febrile illness.

The patient's history is not that of rheumatic pancarditis. Similarly, her illness lacked the stigmata of systemic lupus erythematosus: some arthralgia was present but there were no polyarthritis, serositis, dermatitis, or nephritis. Although dyspnea was present from the onset, the original roentgenogram of the chest was normal, and there were none of the cutaneous or visceral signs or symptoms of progressive systemic sclerosis. Only one of the "collagen" diseases might give rise to the fever, anemia, and dyspnea, and that is polyarteritis nodosa. Pulmonary and coronary arteritis might well be present. Polyarteritis nodosa would not explain the aortic insufficiency. There is lacking, also, any indication that peripheral, renal, gastrointestinal, or central nervous system arteries were involved.

One is compelled to consider the unusual forms of inflammatory and granulomatous aortitis. The course of this patient's illness is different from the natural histories of Takayasu's pulseless disease of young women, and the varied descriptions of giant cell arteritis and aortitis. There are two descriptions of granulomatous and necrotizing aortitis, leading to aortic valvular insufficiency, which seem consonant with the illness of our patient. The first is that of McGuire, Scott and Gall.[1] Their patients had severe disease of the entire aorta down to the level of the diaphragm, with distortion and destruction of the valves, causing aortic incompetence. The second description is that of Pirani and Bennett[2] of the aortitis accompanying rheumatoid spondylitis. One of their cases had not only severe granulomatous aortitis but also a systemic arteritis which resembled periarteritis nodosa. Our patient, obviously, did not have rheumatoid spondylitis. The point of interest is the association of a destructive aortitis with systemic arteritis.

These two descriptions of granulomatous and necrotizing aortitis seem to explain best the natural history of our patient's disease: the fever, the anemia, the coronary artery insufficiency, and progressive aortic valvular insufficiency. I believe that the postmortem examination will reveal an obliterative vasculitis of the vasa vasorum of the aorta, with secondary granulomatous necrosis of the intima and media extending into the bases of the aortic valve, and furthermore, that there is an obliterative coronary vasculitis with myocardial infarction, and

rupture of either the main right renal artery or one of its principal branches. Pulmonary and generalized arteritis may be present. Although there are no signs of systemic arteritis, the dyspnea, the fever, and the anemia lead one to consider this inflammatory disease to be diffuse.

DR. KRAKOWER: She was a frail young woman who was 5 feet tall and weighed 81 pounds. There was pitting edema of both feet and ankles. The serous cavities presented smooth serosal surfaces. The peritoneal cavity contained 100 c.c. of clear yellow fluid, the right pleural cavity 125 c.c., the left pleural cavity 50 c.c., and the pericardial sac 25 c.c.

The heart weighed 480 grams and appeared to be considerably enlarged in situ. The right atrium was small. There were mural thrombi between the pectinate muscles. The tricuspid valve measured 10 cm. in circumference, and its leaflets were normal. The right ventricle was not enlarged but there was some thickening of the trabeculae carneae and slight thickening of the ventricular wall, which measured 0.3 cm. near the pulmonic valve. The latter measured 7.5 cm. in circumference and its cusps were normal. The pulmonary artery and its main branches, although of normal caliber or even a little smaller than normal, presented thickened, leathery walls which were as much as 0.3 cm. in thickness. The intima was largely smooth, but in areas was pitted and ridged. The left atrium was of normal size, with a thrombus filling the auricular appendage. The mitral valve was 8.0 cm. in circumference and had normal leaflets except for three thin, yellow patches of atheroma in the anterior leaflet. The left ventricle was appreciably enlarged, with, if anything, some thinning of papillary muscles and trabeculae carneae, although the myocardium seemed relatively thick, and was 1.1 cm. in thickness near the base of the inflow tract. The endocardium was smooth, with no subaortic ridges or endocardial pockets. The aortic valve measured 7.0 cm. in circumference, but although the leaflets were thin and translucent, they were held so tautly at their attachment that it appeared as though in life they had been unable to expand to close the orifice completely. The commissures, however, were not widened. The sinuses of Valsalva were of normal depth but their aortic walls were characterized by marked thickening which had led to prominent vertical ridging of the intimal surface. No atheromatous lesions were seen. The coronary orifices were slightly narrowed. The right one was situated just within the sinus, 1.7 cm. from the aortic ring. The left one was high, well above the cusp, some 2.0 cm. above the ring. The left descending coronary artery and the dominant right one were leathery firm, thick-walled structures for their greater length. The lumina of these vessels were narrowed but the intimal surfaces were smooth and free of atheroma. The left circumflex branch revealed a thin wall, and smooth, nonatheromatous intima. The myocardium was firm, with an area of necrosis, 0.5 cm. in diameter, in the interventricular septum just beneath the aortic valve.

The arch of the aorta was somewhat dilated, and was as much as 10.0 cm. in circumference in its mid-ascending portion. However, it narrowed to 6.0 cm. in circumference in the mid-thoracic region, and to 4.0 cm. in the mid-abdominal region. For its whole length, and including variable stretches of its major branches, the aorta was characterized by its thickness and amazing leatheriness and inelasticity. The wall of the aorta, in places, was as much as 0.4 cm. in thickness.

Its intimal surface was totally irregular, with a puckered, pitted appearance, associated with an irregular patterning of furrows which ran transversely, obliquely, and at times longitudinally. No yellow atheromatous areas were recognizable. Only in one area in the ascending arch was there a patch, 2.0 by 1.5 cm. in size upon which there was a thin deposit of thrombotic material. The orifices of intercostal and lumbar branches seemed to be deeply set, rather narrow, and less conspicuous than normally.

The lungs were somewhat distended, and nodular to the feel. The right lung weighed 520 grams, and the left one weighed 490 grams. Abundant pink frothy fluid escaped from the cut surfaces, leaving in all, however, a pink firm parenchyma. The tracheobronchial tree was relatively clear, with pink mucosa. The distal branches of the pulmonary arteries were not remarkable. There were no emboli. The tracheobronchial lymph nodes were mildly hyperplastic, and one hilar node was almost totally caseous. (Cultures and smears of lung and hilar lymph node failed to reveal any acid-fast bacilli.)

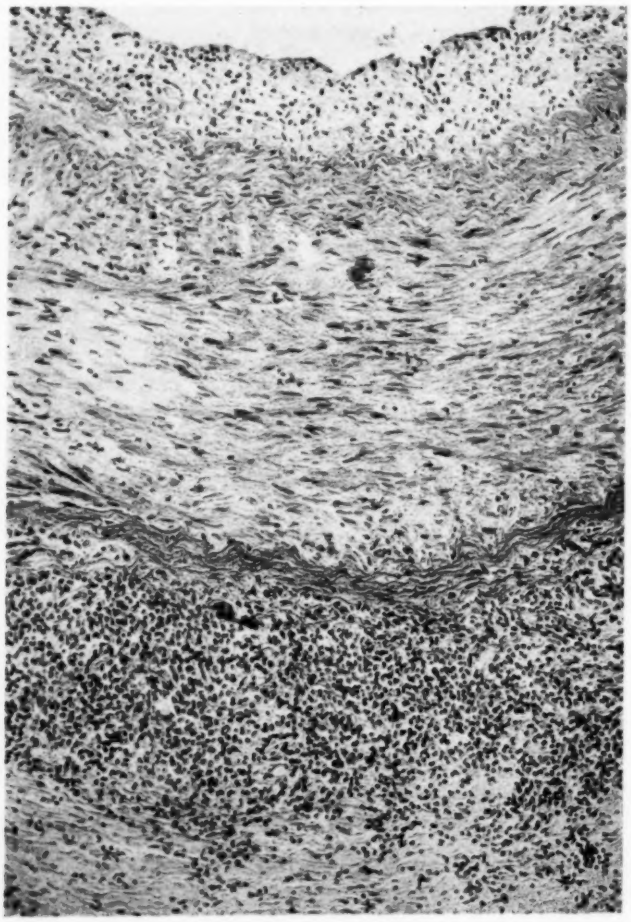

Fig. 3.—Note the heavy cellular infiltrate in the adventitia, with little involvement of media. There is mild intimal cellular infiltration and fibrous thickening. (Hematoxylin-phloxine-saffron stain; ×150, reduced ⅓.)

The right kidney weighed 150 grams, and the left one weighed 140 grams. The capsules were stripped with difficulty, exposing pink surfaces on which were puckered and punctate scars. The cortices averaged 6.0 mm. in thickness, with distinct markings. The medulla of the left kidney was pink, whereas that of the right was red. The upper pole of the right kidney was a dark, dirty pink color, and a branch of the right renal artery which led to this pole was occluded by a fresh thrombus.

With regard to the other organs, the liver was markedly congested, with some diaphragmatic adhesions. The capsule of the spleen was thickened and adherent to surrounding structures. The body of the uterus and the ovaries were atrophic. The cervix was scarred, with a patulous external os. The other organs, including brain and spinal cord, were not remarkable grossly.

Microscopic examination confirmed the presence of myocardial necrosis which was associated with relatively early reactive and repair processes. In

Fig. 4.—Note irregular linear vascularized infiltrate in the media, with prominent dilated vessels in the fibrous adventitia. Note too the extension of dilated vessels into the basal portion of the markedly thickened intima. There is a layer of fibrinoid over the surface of the intima. (Hematoxylin-phloxine-saffron stain; ×53, reduced ⅓.)

addition, there was a patch of endocarditis in the left auricular endocardium. The vascularized inflammatory infiltrate lay deep in the endocardial layer and resembled the arterial infiltrates described below.

The arteries, including the whole of the aorta and its major branches and also the pulmonary artery and its major branches, presented most profound changes. The lesions were of varying intensity and, presumably, duration. They were characterized, in active lesions, by a highly vascular and cellular infiltrate of the adventitia and media, and rarely of the adventitia alone. This infiltrate was composed chiefly of lymphocytes and plasma cells but included variable numbers of polymorphonuclears, eosinophils, and histiocytes. There were very few giant cells, and these were intimately associated with fragments of sequestrated elastic tissue (Figs. 3 and 4). As the lesion aged, more fibroblasts and fibrous tissue appeared, which resulted in inactive lesions with profound thickening and fibrosis of the adventitia and total replacement of the media by scar tissue. It should be indicated that, commonly enough, the adventitial infiltrate was diffuse in the inner layers closer to the media and more perivascular in the outer layers of the adventitia. Furthermore, the vasa vasorum showed little if any intimal changes. They were patent and wide, and, in fact, the striking feature was the high degree of vascularity of the active lesion. Small thick-walled arteries that might be mistaken for sclerosed vessels turned out to be, on more careful inspection, "sperrarterien" with longitudinally directed smooth muscle fibers in their intimal coat. In the media, the vascularized cellular infiltrate and subsequent fibrosis led to partial (Fig. 5) or, in places, total destruction of the elastic laminae in the aorta and the elastica interna and elastic fibers in its branches. The fibrosed media of the aorta, in places, was reduced to a rather thin, homogeneous, fibrous layer, whereas in other areas and in the peripheral arteries the fibrosed media tended to maintain its thickness. Remnants of the elastica, particularly the internal layer, showed splitting fragmentation and, sometimes, calcification. The intima was markedly thickened in most sections in which lesions of media and adventitia were advanced. The thickening was due principally to the deposition of fibrous tissue with a rich component of acid mucopolysaccharides, as shown by the Alcian blue stain. Goodly amounts of proliferation of smooth muscle cells was associated with the fibrous intimal thickening. There was, however, little new formation of elastic tissue. The thick intima was penetrated by capillaries for a very short distance from the involved media, with, at times, a cellular infiltrate. For the most part, however, the thick intima appeared to be avascular. No atheromatous deposits or necrosis were seen in this layer. There was a deposit of fibrinoid material in a section through the ascending aorta in which thrombotic-like deposition was described grossly. In the branch of the renal artery described above, an occlusive fresh thrombus was seen, possibly an embolus from the thrombus in the left auricular appendage. In keeping with the latter, the changes described in the upper pole of the right kidney were microscopically those of an early infarct. The thick intima encroached upon the lumen, but only in a few major coronary arterial branches did it effectively narrow it (Fig. 6).

The lungs were the seat of marked chronic passive congestion. There was a rich proteinaceous fluid, together with fibrin, filling the air spaces. This was asso-

ciated in numerous foci with fibroblastic organization of the exudate. There were a few fresh thrombi, probably emboli, in very small pulmonary arterial branches. There were chronic passive congestive changes in the abdominal viscera, with the following added features: in the spleen, slight periarteriolar fibrosis, depletion of lymphoid tissue, and in one trabecular artery concentric fibrous intimal thickening with adventitial round celled infiltration; in the gall bladder, marked adventitial fibrous and edematous thickening.

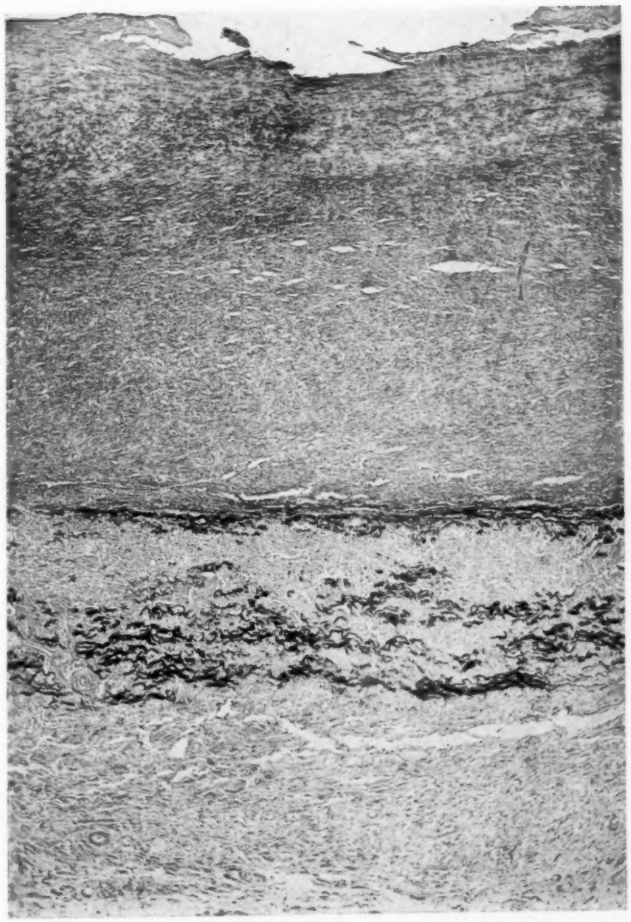

Fig. 5.—An elastic tissue stain which shows the disruption and loss of elastic tissue in the media as well as the absence of elastic tissue in the markedly thickened intima. (Weigert-Van Gieson stain; ×58, reduced ⅓.)

The immediate cause of this patient's death could be accounted for by two factors. The first was related to the aortic inflammatory changes at the base of the aorta. It may be assumed on morphologic grounds that, although the aortic ring was not widened, and although there was neither separation of the commissures of the cusps nor involvement of the cusps proper, the sclerosing aortic process was such as to narrow the space or capacity of the sinuses of Valsalva, to render the aortic walls of the sinuses so rigid and inelastic, and to draw the cusps so tightly against the aortic wall that they no longer could approximate in diastole.

There was, therefore, a regurgitant central stream of blood with no ensuing subaortic endocardial thickening or pockets. Coupled with the aortic regurgitation and the narrowing and inelasticity of the coronary arteries, there was a degree of coronary insufficiency adequate to produce subaortic basal myocardial infarction terminally. There were resultant evidences of myocardial failure with pulmonary and visceral passive congestion. Secondly, there were diffuse, predominantly serous, inflammatory changes in the lungs, associated with multiple areas of organizing pneumonitis.

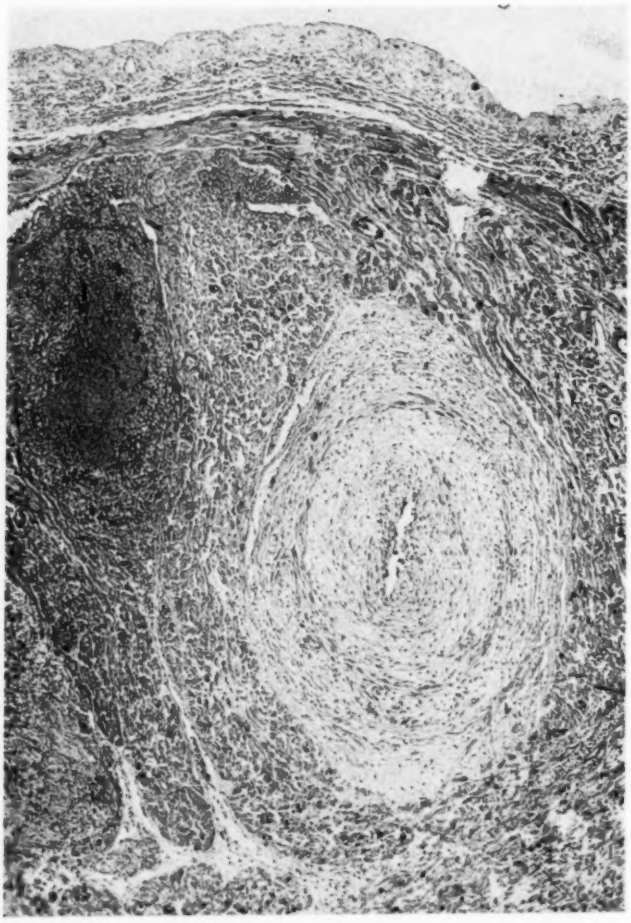

Fig. 6.—Branch of the coronary artery in the wall of the auricle, showing profound fibrous intimal thickening with luminal narrowing. The media is disrupted by fibrous tissue which extends to involve the thick adventitial coat. (Hematoxylin-phloxine-saffron stain; ×80, reduced ⅓.)

The essential disease process in this case was, therefore, one of a diffuse peri- and mesaortitis and pulmonary arteritis, with extension to involve the major divisions of these arteries. The various forms of inflammatory vascular disease, such as polyarteritis nodosa, hypersensitivity angiitis, and those associated with such "collagen" diseases as lupus erythematosus, scleroderma, and even rheumatoid arthritis, do not appear to pertain to this case. The involvement in these

diseases is pre-eminently that of small arteries, arterioles, or even capillaries and venules, and they are associated with sharper necrotizing processes, fibrinous deposition, and thromboses than was the case here. Of those inflammatory diseases which involve larger vascular sectors more diffusely, thromboangiitis obliterans with its prominent venous involvement can be excluded. Giant cell arteritis occurs in a much older age group and, as a rule, involves temporal, occipital, and other cranial arteries even though it may involve arteries elsewhere more diffusely. Morphologically, too, it differs somewhat from the lesions in the present case in that the outer intima and inner media are more markedly involved by the inflammatory process, patchy areas of necrosis are present, and the adventitia may show little involvement. Giant cells are more abundant in active lesions. The only angiitis to be considered due to a known microorganism, viz., syphilis, can probably be excluded because of the lack of significant changes in the vasa vasorum, the absence of gummata and necroses, the high degree of vascularity of the active lesions, as well as for other reasons detailed in McGuire, Scott and Gall's paper.[1] The clinical and morphologic changes of this case match those of the five cases described by McGuire and associates, of chronic aortitis of undetermined cause. They differ, however, in that: (1) the disease in the present case involved all portions of the aorta and the pulmonary artery, and their major branches, such as the coronaries, and was not limited to the aorta from base to diaphragmatic level; (2) there was no aortic valvular involvement, not even commissural separation, whereas such changes occurred in McGuire's cases; and (3) there was a patch of endocarditis in the left auricular endocardium, with reactive changes similar to those in the arteries.

In any attempt to classify the various forms of noninfectious inflammatory angiitis, it should be emphasized that there may be an overlap in the size and distribution of the involved vessels, as well as variations in the reactive processes. Thus, giant cell arteritis may be complicated by polyarteritis[3] or rheumatoid arthritis which involves more commonly smaller vessels by an aortitis. A multiplicity of factors, such as age, duration of the disease, etc., all may modify the extent and character of the angiitis. It is only when the etiology and pathogenesis of these noninfectious inflammatory vascular diseases are more clearly understood that it may then be possible to arrive at a satisfactory classification.

Diagnosis: Diffuse Chronic Aortitis and Pulmonary Arteritis, of Undertermined Etiology, With Involvement of Their Major Branches

REFERENCES

1. McGuire, J., Scott, R. C., and Gall, E. A.: Chronic Aortitis of Undetermined Cause With Severe and Fatal Aortic Insufficiency, Am. J. M. Sc. **235**:394, 1958.
2. Pirani, C. L., and Bennett, G. A.: Rheumatoid Arthritis. A Report of 3 Cases Progressing From Childhood and Emphasizing Certain Systemic Manifestations, Bull. Hosp. Joint Dis. **12**:335, 1951.
3. Ross Russell, R. W.: Giant-Cell Arteritis. A Review of 35 Cases, Quart. J. Med. **28**:471, 1959.

Annotations

Cardiac Glycogenosis

Cardiac enlargement and failure of obscure origin presents a diagnostic challenge which was crystallized by Brigden.[1] Even among the rarer causes of such "cardiomyopathy" the glycogen-storage diseases occupy an unusual position, wherein biochemical analysis has far outstripped their clinical recognition.

Traditionally, two types of glycogenosis were distinguished, according to whether the stored glycogen followed an hepaticorenal or a muscular distribution. The former (Type 1),[2] described in 1929, by Von Gierke,[2] involves normal glycogen with a glucose-6-phosphatase deficiency, and from the 100 or more cases reported it does not appear to present a primary cardiac problem.[3] Even so, the glycogen content of heart muscle may be comparable with that of the liver in some cases.[4] Despite its alleged noncardiac manifestation, death in congestive cardiac failure has been reported.[5] Type 2, the muscular or generalized type of Pompe,[6,7] also involves normal glycogen, but with an unrecognized metabolic defect[8,9] commonly presents as cardiac enlargement. It was first regarded as a variation of Von Gierke's disease but Di Sant' Agnese and colleagues[9,10] showed it to be different both chemically and clinically. The clinical pattern presents, in varying proportions, cardiac enlargement and weakness of skeletal muscle. The latter may closely mimic amyotonia congenita.[11,12] Both show a strong familial incidence,[9,13] possibly transmitted as a sex-linked recessive,[14] but death in infancy, believed to be the invariable outcome,[13] precludes direct analysis of heredity.

Thanks to the biochemical studies of Cori,[4,15] Di Sant' Agnese[3] was able to define three further types of glycogenosis, but the paucity of available information is exemplified by the fact that only some 20 cases of Type 2 have been described and far less is known of the others.

"Limit dextrinosis"[4] (Type 3) is described largely from the biochemical analysis of 9 cases[15] in which a deficiency of the debranching enzyme, amylo-1-6-glucosidase, was found. From the scant clinical data available, hepatomegaly has appeared to be the dominant feature, but some alleged weakness of skeletal muscle and exess myocardial glycogen allows the possibility that a cardiac involvement may occur. A familial incidence is suspected, and regression with age may possibly occur.[16]

Only one case of Type 4 has been fully studied,[17] and the relevant findings were an abnormal glycogen with hepatic enlargement and cirrhosis.

Type 5 is even more nebulous. The one reported case[3] was that of a 2½-year-old child who showed skeletal and palatal muscular weakness and a high incidence of normal glycogen in skeletal muscle.

It may be seen then that even in Von Gierke's disease, which classically does not present as a cardiac problem, there is a heavy deposition of glycogen in the myocardium, and at least terminal cardiac failure is known to occur. To the Pompe type is ascribed primary myocardial failure, but the rarity of the condition and the fact that no cases have been diagnosed during life leaves room for doubt that the condition is of necessity fatal in infancy. Allowing that inadequate knowledge of the other groups permits no definition of their age incidence or prognosis, it is possible that any of the glycogenoses might appear beyond infancy and perhaps into adult life. Whenever myo-

cardial involvement predominates, diagnosis during life is difficult, because indirect histologic confirmation by biopsy of liver or skeletal muscle may be inconclusive unless complicated biochemical analysis is available. Even at autopsy the quantitative evaluation of myocardial glycogen is of no specific value in the diagnosis of glycogen-storage disease,[18] and it is for this reason that a case of alleged cardiac glycogenosis, with the patient surviving to the age of 15 years,[19] has not been regarded as established. Nevertheless, the literature would not seem to provide adequate grounds for disregarding the possibility of glycogenosis of one type or another presenting as "cardiomyopathy" beyond the age of childhood. Firm diagnosis during life will continue to be beset by difficulties until the specific clinical patterns can be more clearly defined.

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REFERENCES

1. Brigden, W.: Uncommon Myocardial Disease, Lancet **2**:1179 and 1243, 1957.
2. Von Gierke, E.: Hepato-nephromegalia glycogenica, Beitr. z. path. Anat. u. z. allg. Path. **82**:497, 1929.
3. Di Sant' Agnese, P. A.: Diseases of Glycogen Storage, With Special Reference to the Cardiac Type of Generalized Glycogenosis, Ann. New York Acad. Sc. **72**:439, 1959.
4. Cori, G. T.: Glycogen Structure and Enzyme Deficiencies in Glycogen Storage Disease, Harvey Lectures **48**:145, 1952.
5. Mason, H. H., and Andersen, D. H.: Glycogen Disease of the Liver (Von Gierke's Disease) With Hepatomata, Pediatrics **16**:785, 1955.
6. Pompe, J. C.: Over diopatische hypertrophie van het hart, Nederl. tijdschr. geneesk. **76**:304, 1932.
7. Bischoff, G.: Zum klinischen Bild der Glykogen-Speicherungskrankheit (Glykogenose), Ztschr. Kinderh. **52**:722, 1931-32.
8. Hauk, R., Illingworth, B., Brown, D. H., and Cori, C. F.: Enzymes of Glycogen Synthesis in Glycogen-Deposition Disease, Biochim. et biophys. acta **33**:554, 1959.
9. Di Sant' Agnese, P. A., Andersen, D. H., Mason, H. H., and Bauman, W. A.: Glycogen Storage Disease of the Heart, 1, Pediatrics **6**:402, 1960.
10. Di Sant' Agnese, P. A., Andersen, D. H., and Mason, H. H.: Glycogen Storage Disease of the Heart, 2, Pediatrics **6**:607, 1960.
11. Clement, D. H., and Godman, G. C.: Glycogen Disease Resembling Mongolism, Cretinism and Amyotonia Cogenita, J. Pediat. **36**:11, 1950.
12. Krivit, W., Polglase, W. J., Gunn, F. D., and Tyler, F. H.: Studies in Disorders of Muscle; Glycogen Storage Disease Primarily Affecting Skeletal Muscle and Clinically Resembling Amyotonia Congenita, Pediatrics **12**:165, 1953.
13. Friedman, S., and Ash, R.: Glycogen Storage Disease of the Heart, J. Pediat. **52**:635, 1958.
14. Landing, B. H., and Bangle, R.: Glycogen Storage Disease, J. Tech. Methods **31**:84, 1950.
15. Illingworth, B., Cori, G. T., and Cori, C. F.: Amylo-1-6-Glycosidase in Muscle Tissue in Generalized Glycogen Storage Disease, J. Biol. Chem. **218**:123, 1956.
16. Forbes, G. B.: Glycogen Storage Disease, J. Pediat. **42**:645, 1953.
17. Andersen, D. H.: Familial Cirrhosis of the Liver With Storage of Abnormal Glycogen, Lab. Invest. **5**:1, 1956.
18. Mowry, R. H., and Bangle, R.: Histiochemically Demonstrable Glycogen in the Human Heart, Am. J. Path. **27**:611, 1951.
19. Antopol, W., Boas, E. P., Levison, W., and Tuchman, L. R.: Cardiac Hypertrophy Caused by Glycogen Storage Disease in a Fifteen-Year-Old Boy, AM. HEART J. **20**:546, 1940.

The Dreamers and the Skeptics

"Man proposes and God disposes," but let us remember that the disposing is done by God. The skeptics and debunkers in our scientific midst, in performing their rightful tasks, may confuse their opinions with what in the last analysis must be the collective judgment of mankind over the years.

It has been the unhappy history of science that new advances have often been bitterly opposed by contemporary academicians, whatever the form their institutions may have taken at any given time. On the other hand, it is necessary to protect science or medicine from the prevaricators, and from the prejudiced, unsound, or mistaken thinkers. Today, however, we do not burn our

Servetus at the stake or make our Gallileo recant. Instead, we direct scientific invective at him in journals or from platforms, and we whisper behind the hand to our colleagues at cocktail parties.

As our civilization advances, however, and moral behavior becomes the rule, it becomes less important to lift the lance against dwindling quackery and nostrums. The conflicts of today usually arise between scientists who differ only because they investigate different aspects of the same problem. However vital to the advance of science may be the agreement or lack of agreement between such scientists, negative results in experiments which do not duplicate the original experiments and in which different methods or subjects are used cannot be invoked in refutation. The design of such negative experiments often demonstrates a rigid attachment to some theory or doctrine which presumably has been violated. What is more, when some new aspect of knowledge is confirmed by our academicians, recognition often appears to be given grudgingly and ungraciously.

Let us then accept the honest dreamers in our midst and encourage them. If we disagree, let their experiments be repeated exactly and their experiences confirmed or denied. If they are denied, let us be charitable and not assassinate their reputations; and if confirmed, let us do honor to these men. Surely we have learned enough from the history of nations, religion, and science to abandon all inquisitions.

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Cerebral Anoxia

The primary function of the heart is to maintain an adequately oxygenated supply of blood to the brain. Absolute cardiac failure, therefore, results in death, and intermittent, or partial, failure may produce a state of temporary suboxygenation which is harmful. Severe, intermittent cerebral anoxia in the form of cerebral ischemia can occur in Adams-Stokes attacks, from inadvertent cardiac arrest, which subsequently returns to normal, or during deliberate exclusion of the heart from the circulation during certain cardiac operations.

The length of time that the human brain will withstand ischemia has, for obvious reasons, never been established satisfactorily. Experimentally, times as short as 3 minutes and 10 seconds in the cat,[1] and as long as 8 minutes in the dog,[2] have been shown to produce histologic changes in the brain. In man, the commonly accepted safe length of time is 4 minutes,[3,4] although extensive cerebral damage has been reported from cardiac arrest of this duration.[5] But the amount of cerebral damage is not entirely related to the length of time. The older the subject the shorter the safe period, and the pharmacologic or physiologic state of the brain when the insult occurs is also a factor. Hypothermia, on the other hand, protects the brain from cerebral ischemia and is now used extensively for this purpose in neurosurgery and cardiac surgery. In these two surgical fields evidence is accumulating in regard to the time that the human brain can tolerate ischemia without ill effects; it is now generally conceded that total cerebral circulation can be occluded for up to 10 minutes at 30°C. with safety,[6] and at 15°C. full recovery has been recorded after 45 minutes of complete ischemia.[7] A further factor in the incidence of cerebral damage after ischemia is the possibility of intravascular clotting which occurs because of stagnation in the smaller blood vessels during the ischemic period.[8] There is some support for this hypothesis in as much as the ischemic time can be increased in the human being at normal temperature by prior heparinization.[9]

Whether repeated periods of anoxia can cause permanent damage has not yet been proved. Some authors[10,11] have demonstrated histologic changes in animals subjected to repeated anoxic insults for short periods, but later work[12] has failed to confirm these observations. However, these latter authors did show that animals which were subjected to multiple doses of anoxia over a short period of time were neurologically abnormal for some days following the experiments. Clinically, absolute proof, one way or the other, is lacking because of the fact that man is unlikely to tolerate a state wherein intermittent bouts of acute anoxia occur. The only possible tolerance of such circumstances would be in a patient suffering from Wolff-Parkinson-White syndrome, and so far no histologic or psychologic studies have been reported on such patients.

The immediate treatment of acute cerebral ischemia is obvious, namely, the restoration of the circulation. There is general agreement now that this is best achieved by manual cardiac massage performed through the chest. Once the circulation to the brain has been re-established, efforts must be made to minimize the damage to the brain caused by the ischemia. Cerebral anoxia of any type is always followed by a state of intracellular edema, which, if allowed to persist, may either cause destruction of the cells or prevent them from functioning normally.[12] Treatment must, therefore, be directed toward reducing this intracellular edema; at the same time, a reduction in the demand for oxygen and in general metabolism is advantageous, because this allows the cell to rest and regain its normal function slowly. The combination of dehydrating agents, such as 50 per cent sucrose or concentrated plasma, and hypothermia to 32°C. is now the accepted form of therapy for the treatment of the postanoxic state.[13]

Chronic cerebral anoxia may often accompany cardiac failure, and the suboxygenation may present as nightmares and restlessness at night and as an anxiety state during the day. The administration of hypotensive drugs, too, can, under certain circumstances, produce a chronic anoxic state.[14] The condition, however, does not arise in patients with congenital cyanotic heart disease. Such patients have a poor cardiorespiratory reserve, but there is no evidence of anoxia at rest; they are not mentally retarded or psychotic, as one would expect if they suffered from chronic anoxia.[15]

The recognition of chronic anoxia may have to depend upon estimations of arterial oxygen. Clinical observations, particularly the noting of the presence or absence of cyanosis, may be misleading. Confirmation of the condition, however, can often be obtained by the administration of 100 per cent oxygen via an accurately fitting face mask for several hours. If the subject has been anoxic, the symptoms, particularly restlessness, will disappear. The administration of oxygen is of great value in the treatment of the sleeplessness which occurs with chronic anoxia, as was proved during the last British expedition up Mount Everest, when the anoxia due to the high altitude prevented sleep and thereby exhausted the climbers.[16] Sedatives for controlling the restlessness or anxiety are not to be recommended, but may have to be given in small doses in order to diminish total body activity, which may otherwise increase the demands of the body for oxygen, thus worsening the condition. In theory, an increase in the efficiency of the tissue oxygen-enzyme system should be advantageous, and cytochrome-C has been advocated for this purpose,[17] but the results have been equivocal, and so far no other tissue enzymes have been found to be of any value. One other way of treating the condition would be to enhance the flow of blood to the brain by means of some extracorporeal circulation, or to increase the oxygen tension of the circulating blood by placing the patient under high-pressure oxygen. The former has been demonstrated to be feasible in animals, and has been suggested as a treatment of cardiac failure.[18] The latter has yet to be tried, but may become possible now that experience is being gained with high-pressure oxygen for radiotherapy.[19]

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REFERENCES

1. Weinberger, L. M., Gibbon, M. H., and Gibbon, J. H., Jr.: Temporary Arrest of the Circulation to the Central Nervous System. II. Pathological Effects, Arch. Neurol. Psychiat. **43**:961, 1940.
2. Kabat, H., Dennis, C., and Baker, A. B.: Recovery of Function Following Arrest of the Brain Circulation, Am. J. Physiol. **132**:737, 1941.
3. Johnson, J., and Kirby, C. K.: Cardiac Resuscitation, Surg. Clin. North America **29**:1745, 1949.
4. Stephenson, H. E., Jr., Reid, L. C., and Hinton, J. W.: Pitfalls, Precautions and Complications in Cardiac Resuscitation, Ann. Surg. **137**:731, 1953.
5. Mandel, M. M., and Berry, R. G.: Human Brain Changes in Cardiac Arrest, Surg. Gynec. & Obst. **108**:692, 1959.
6. Ross, D. N.: Hypothermia as an Aid to Surgery, Ann. Roy. Coll. Surgeons England **24**:43, 1959.
7. Drew, C. E., and Anderson, I. M.: Profound Hypothermia in Cardiac Surgery. Report of Three Cases, Lancet **1**:748, 1959.
8. Crowell, J. W., Sharpe, G. P., Lambright, R. L., and Read, W. L.: The Mechanism of Death After Resuscitation Following Acute Circulatory Failure, Surgery **38**:696, 1955.

9. Orton, R. H., and Morris, K. N.: Deliberate Circulatory Arrest. The Use of Halothane and Heparin for Direct-Vision Intracardiac Surgery, Thorax **14**:39, 1959.
10. Tannenberg, J.: Comparative Experimental Studies on Symptomatology and Anatomical Changes Produced by Anoxic and Insulin Shock, Proc. Soc. Exper. Biol. & Med. **40**:94, 1939.
11. Thorner, M. W., and Lewy, F. H.: The Effects of Repeated Anoxia on the Brain. A Histopathology Study, J.A.M.A. **115**:1595, 1940.
12. Lucas, B. G. B., and Strangeways, D. H.: The Effect of Intermittent Anoxia on the Brain, J. Path. Bact. **44**:265, 1952.
13. Lucas, B. G. B.: Anoxic States and Their Treatment. Modern Trends in Anaesthesia (edited by F. T. Evans and T. Cecil Grey) London, 1958, Butterworth & Co., p. 284.
14. Nilsson, E.: The Application of a Method for the Investigation of Cerebral Damage Following Anaesthesia Using Controlled Hypotension, Brit. J. Anaesth. **25**:24, 1953.
15. Lucas, B. G. B.: Resuscitation of the Newborn, Proc. Roy. Soc. Med. **43**:449, 1950.
16. Pugh, L. G. C.: The Physiology of Man at High Altitudes. The Effects of Oxygen on Acclimatized Man at High Altitude, Proc. Roy. Soc. London, ser. B. **143**:14, 1954.
17. Proger, S., and Dekaneas, D.: Cytochrome-C in Combating Tissue Anoxia, Science **104**:389, 1946.
18. Connolly, J. E., Bacaner, M. B., Bruns, D. L., Lowenstein, J. M., and Storli, E.: Mechanical Support of the Circulation in Acute Heart Failure, Surgery **44**:255, 1958.
19. Emery, E. W., Lucas, B. G. B., and Williams, K. G.: Technique of Irradiation of Conscious Patients Under Increased Oxygen Pressure, Lancet **1**:248, 1960.

The Lead Tensor: Its Nature and Prospective Applications

It is common practice in electrocardiographic analysis to idealize the human body into a homogeneous volume conductor, and the heart itself into one or more dipolar generators of electrical current. Within this framework of idealization it is possible to represent the physical characteristics of a given electrocardiographic connection as a lead vector, and the difference in potential across the connection as one or more scalar products of heart and lead vectors.

Since a current dipole is a first-order electrical singularity, the above-mentioned idealization of heart-lead relationships is, in a certain sense, a first-order approximation. In order to improve the excellence of approximation, there has been considerable interest recently in the possibility of representing the electrical activity of the heart as superposed singularities of several orders, such as dipole + quadripole + octapole + multipoles of still higher order.[1] This concept appears worthy of serious consideration since, at least in principle, it can be made to account accurately for the electrocardiographic potential developed at any point on the body surface.

The lead vector does not apply directly to current multipoles. However, it has proved so useful in relation to the current dipole that we have undertaken to discover whether analogous, higher-order lead parameters exist which might be similarly applied to equivalent cardiac multipoles. Our initial explorations have produced some interesting developments, which will be recounted briefly in this communication.

In the case of the equivalent cardiac dipole the potential across a lead connection is frequently written as $V = \mathbf{H} \cdot \mathbf{F}$, where **H** is the heart vector, and **F** the lead vector. The same expression can be written in the somewhat more perspicuous form, $V_{(1)} = H_{(1)}\, a^i F_i$ $(i = 1,2,3)$, where $H_{(1)}$ is the magnitude of the heart vector, the a^i are the direction cosines of the heart vector, and the F_i are the components of the lead vector. We find that higher-order cases can be expressed as:

$$V_{(2)} = H_{(2)} A^{ij} F_{ij} \; (i,j = 1,2,3),$$
$$V_{(3)} = H_{(3)} A^{ijk} F_{ijk} \; (i,j,k = 1,2,3),$$
$$V_{(4)} = H_{(4)} A^{ijkl} F_{ijkl} \; (i,j,k,l = 1,2,3), \text{ etc.}$$

The foregoing equations are written in conventional tensor notation. For instance, A^{ijkl} is a contravariant tensor of the fourth rank, whereas F_{ijkl} is a covariant tensor of like rank. The respective covariant and contravariant indices (i,j,k,l) are identical. According to the laws of tensor algebra, the product of the two is a scalar quantity. Multiplication of the A^{ijkl} by $H_{(4)}$ gives a somewhat different contravariant tensor, M^{ijkl}, which expresses the components of the electrical multipole. In this respect it is quite analogous to the lower-order case, $M^i(x,y,z)$, which gives M_x, M_y, M_z as the components of a heart vector. In this sense we refer to M^{ijkl} as a *heart tensor* of the fourth rank. The covariant expression of like rank, F_{ijkl}, we call the *lead tensor*.

The $A^{ijkl.....nth\ term}$ are formed by successive tensor multiplication of the direction cosines, a^i, b^j, c^k, etc., which specify the distribution of the multipole elements. Accordingly, $A^i = a^i$, $A^{ij} = -a^ib^j$, $A^{ijk} = a^ib^jc^k$, ..., $A^{ijk.....nth\ term} = (-1)^{n-1}a^ib^jc^k$.....nth term.

The $F_{ijkl.....nth\ term}$ represent higher-order lead parameters, which are obtained by successive partial differention of a conservative potential function, ϕ. Specifically, $F_i = \partial\phi/\partial x^i$, $2!F_{ij} = \partial^2\phi/\partial x^i\partial x^j$, $3!F_{ijk} = \partial^3\phi/\partial x^i\partial x^j\partial x^k$, etc.

In the first-order case the F_i are $\partial\phi/\partial x$, $\partial\phi/\partial y$, and $\partial\phi/\partial z$, which are recognized as the components of the lead field gradient.[2] This observation is of fundamental importance since it clearly indicates that the lead field can be generalized to include the case of multipolar electrocardiographic generators. In brief, it is the higher-order lead parameters from which lead tensors are formed.

As is the case with many other physical problems of a complicated nature, the tensor apparatus describes the laws of electrocardiographic leads with great force and compactness. The lead tensor serves a dualistic function. On the one hand, as an abstract symbol it obeys various laws of tensor mathematics. On the other hand, it serves to "program," or specify, a number of operations which are to be performed. For instance, a lead tensor of the nth rank directs that 3^n partial derivatives of the nth order shall be determined. Because these terms depend upon combinative rather than permutative principles, the actual number of terms is reduced to $\frac{1}{2}(n + 2)(n + 1)$. Of these, $\frac{1}{2}n(n - 1)$ are redundant because the lead field is conservative, leaving only $2n + 1$ terms necessary to define the lead tensor. Interestingly enough, this figure agrees exactly with the minimum number of terms which are required to define the components of an nth order multipole.[3] However, determination of the product, $V_{(n)}$, requires that 3^n individual product-terms be calculated and summed.

In essence, the lead tensor provides a method for divorcing intrinsic lead characteristics from the heart itself, whether cardiac representation be in the form of a cardiac multipole or an equivalent electromotive surface. Herein lies its merit as a prospective research tool, for it is our present belief that it will prove quite feasible to determine the lead tensors of the body by direct experimental procedures performed on torso models. Since past and present studies of lead vectors (i.e., lead tensors of the first rank) have added much to the science of electrocardiography, we trust that future studies of higher-order lead parameters will contribute further information.

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REFERENCES

1. Geselowitz, D. B.: Multipole Representation for an Equivalent Cardiac Generator, Proc. Inst. Radio Engineers **48**:75, 1960.
2. Brody, D. A., and Romans, W. E.: A Model Which Demonstrates the Quantitative Relationship Between the Electromotive Forces of the Heart and the Extremity Leads, Am. Heart J. **45**:263, 1953.
3. Stratton, J. M.: Electromagnetic Theory, New York, 1941, McGraw-Hill Book Company, Inc.
4. Brody, D. A., Bradshaw, J. C., and Evans, J. W.: The Elements of an Electrocardiographic Lead Tensor Theory, Bull. Math. Biophysics. (December, 1960. In press.)

Book Reviews

DIE NERVALE UND HORMONALE REGULATION DES BLUTKREISLAUFS (Verhandlungen der Deutsche Gesellschaft für Kreislaufforschung). Edited by Prof. Dr. Rudolf Thauer, Bad Nauheim and Giessen. Darmstadt, 1959, Dr. Dietrich Steinkopff Verlag, 338 pages, 139 illustrations. Price DM 46.

The subject of the 25th annual meeting of the Deutsche Gesellschaft für Kreislaufforschung was "the neural and hormonal regulation of circulation." During the introduction, Dr. Thauer, as President, discussed actual questions in the development of biology and medicine. Cardiology as an independent special field of research was noted.

The scientific session was opened by Dr. Wagner, of München, who discussed general principles in the regulation of the circulation. These were compared with the control and computor systems as they are used in physics. From this point of view new correlations were recognized and different circulatory events were reduced to common principles. Dr. Orthmann, of Frankfurt, discussed the general anatomy of the nervous supply to the vascular system and pointed out that modern investigations by means of electron-microscopy and biochemistry have confirmed and deepened previous knowledge concerning the innervation of this system.

Dr. Holtz, of Frankfurt, gave a report on the physiology of neural and hormonal regulation of circulation, paying special attention to the adrenergic-cholinergic balance system.

Dr. Oberholzer, of Zürich, spoke about the centers in the central nervous system which influence the circulation and pointed out that these centers should be regarded as functional units.

Dr. Folkow, of Göteborg, showed the special adaptation possibilities of the circulation.

The papers which followed dealt with correlations between blood pressure and the suprarenal hormones. Dr. Braach then spoke about a substance to be found in the splenic-venous blood which has a vasopressor effect on arterial pressure, a vasodepressor effect on venous pressure, and an indifferent effect on the heart rate.

The second day of the conference was started by Dr. Neill, of London, who spoke about the afferent innervation of the arterial system. Dr. Kramers, of Baumgarten (Göttingen), Dr. Kalkhoff, of Halle, and Dr. Pellegrino, of Pavia, contributed information regarding these same problems and also the cardiovascular reflexes.

Neural and humoral dysfunctions from the clinical point of view were discussed by Dr. Mechelke, of Heidelberg, and Dr. Schwiegk, of München.

EKG—FIBEL. By Priv.-Doz. Dr. Rolf Heinecker, I. Medizinische Univ.-Klinik, Frankfurt-am-Main, with a foreword by Prof. Dr. Ferdinand Hoff, Frankfurt-am-Main. Fourth enlarged edition, Stuttgart, 1960, Georg Thieme Verlag, 235 pages, 364 illustrations. (Available in U.S.A. and Canada: Intercontinental Medical Book Corporation, New York, N. Y.).

The author of this introduction to electrocardiography is director of the electrocardiographic service of the I.University Hospital in Frankfurt-am-Main, and the numerous illustrations contained in this book are based on the electrocardiographic files of this hospital. These electrocardiograms have all been registered with a photographic type of high-frequency instrument in sets of three synchronous leads, together with the heart sounds. The present fourth edition of the book

was completely revised, and includes a more detailed treatment of the electrocardiogram in electrolyte imbalance and in congenital and valvular heart disease. Practically important diagnostic points are stressed throughout. The book is provided with a short selected bibliography.

PATHOGENESIS AND TREATMENT OF OCCLUSIVE ARTERIAL DISEASE (Proceedings of a Conference held in London at the Royal College of Physicians of London, Nov. 13-14, 1959). Edited by Lawson McDonald, London, 1960, Pitman Medical Publishing Company, Ltd., and Philadelphia, 1960, J. B. Lippincott Company, 237 pages. Price $5.00.

This book contains numerous drawings and photographs. Some of the photographs of sections of arteries are of poor quality, whereas others, such as those of the injected coronary artery, are good. The publication is lithographed on paper of moderate to poor quality.

The material contained in the publication is intended for practicing physicians, and because of this, many of the detailed or technical problems related to the peripheral circulation have been avoided. The participants in the conference included about 25 well-known British authorities, among whom were physiologists, pathologists, radiologists, histologists, internists, and surgeons.

The general plan of the book is its division into four main subjects: the pathogenesis of occlusive arterial disease, cerebral vascular disease, coronary artery disease, and peripheral vascular disease. For the most part, the papers are of the review type; however, they are presented by workers who have had personal experience with the subject. At the end of each section is a discussion, and this feature is probably one of the more important aspects of the book. Each speaker has included a few well-chosen references relative to the subject.

This publication presents some of the important aspects of the pathogenesis and treatment of the occlusive arterial diseases, and it should be useful for internists because it provides up-to-date, concise information relative to the subject.

A PRIMER OF ELECTROCARDIOGRAPHY. Fourth Edition. By George E. Burch, M.D., F.A.C.P., Henderson Professor of Medicine, Tulane University School of Medicine; Physician-in-Chief, Tulane Unit, Charity Hospital; Consultant in Cardiovascular Diseases, Ochsner Clinic, New Orleans; and Travis Winsor, M.D., F.A.C.P., Assistant Clinical Professor of Medicine, University of Southern California Medical School; Director, Heart Research Foundation, Los Angeles, Calif. Philadelphia, 1960, Lea & Febiger, 286 illustrations, 293 pages. Price $5.00.

This extraordinarily durable and useful book is now in its fourth edition (the third appeared in 1955); having gone through 16 reprintings in English, it is now available in French, Spanish, Italian, Turkish, and Serbo-Croatian. It is very much to the authors' credit that the work remains true to its title: it is a primer, and as such is probably the most useful presentation of the subject for the beginner.

The authors' original aim was to lay out the bare fundamentals of electrocardiography, as they stood in 1945, clearly and dogmatically. Controversial matter was to be avoided altogether or given rather cursory treatment. Both aims are carried out intact in the fourth edition. Comparison of the first and fourth editions discloses very little alteration in the first three chapters of the book. Classic electrophysiologic theory is followed in the first chapter; the only new addition is brief mention of the spatial vectorcardiogram and a stereoscopic illustration of normal loops. In the second chapter, components of the standard electrocardiogram, normal and abnormal, are viewed empirically, with deft interweaving of vectorial implications. Helpful new illustrative material has been added. This chapter acquaints the beginning student with the language of clinical electrocardiography with great clarity and deals in a straightforward manner with such troubled areas as bundle branch block and ventricular hypertrophy and or strain. Objections may, of course, easily be raised by proponents of divergent views but it seems highly unlikely that comparisons and contrastings of such views are appropriate for a book of this scope and intent.

The chapter on precordial leads now includes better discussions of unipolar leads in general, and excellent illustrations, in accordance with changes in practice since 1945. Disorders of the heartbeat are adequately covered in the fourth chapter.

The final chapter contains a great deal of practical information and an expansion of earlier material dealing with spatial vectorcardiography. The section is well illustrated and is very circumspect with regard to the clinical usefulness, at the present time, of spatial vectorcardiography. The section should serve quite well to acquaint the student with one of the major directions of electrocardiographic research, without confusing or misleading him inordinately.

Unless one wishes to do battle with the authors over currently debated minutiae of electrocardiographic theory, one finds it difficult to criticize the book. It is an excellent introductory work and, with its appendix, is of considerable help to the more advanced student who must interpret electrocardiograms. One might note, by way of criticism, that the index is not very complete, and that the authors' admonition to the student to dig into source material would be easier to follow if key references were included.

Nonetheless, the new edition, with its improved illustrations and better printing, is likely to be as popular as its predecessors. It can hardly fail to retain its reputation as the most suitable work for the complete beginner in this complex and controversial field.

Announcements

AN ADVANCED COURSE IN THE INTERPRETATION OF COMPLEX ARRHYTHMIAS will be given at Michael Reese Hospital by Louis N. Katz, M.D., Richard Langendorf, M.D., and Alfred Pick, M.D This course is intended only for experienced electrocardiographers. The class will meet daily from 9:00 A.M. to 5:00 P.M., Dec. 5-9, 1960.

Further information may be obtained from the Secretary, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital and Medical Center, Chicago 16, Ill.

INTERPRETATION OF ELECTROCARDIOGRAMS (sponsored by the American College of Physicians) is an intramural continuation course for practicing physicians which is being conducted by the Division of Postgraduate Medical Education at the University of Utah, Salt Lake City, Utah, Nov. 7-11, 1960.

THE WESTERN SOCIETY FOR CLINICAL RESEARCH will hold its Fourteenth Annual Meeting in Carmel-by-the-Sea, Calif., on Thursday afternoon, Friday morning, and Saturday morning, Jan. 26, 27, and 28, 1961.

Information regarding the meeting may be obtained from the Secretary, Western Society for Clinical Research, University of California Medical Center, Department of Medicine, Los Angeles 24, Calif.